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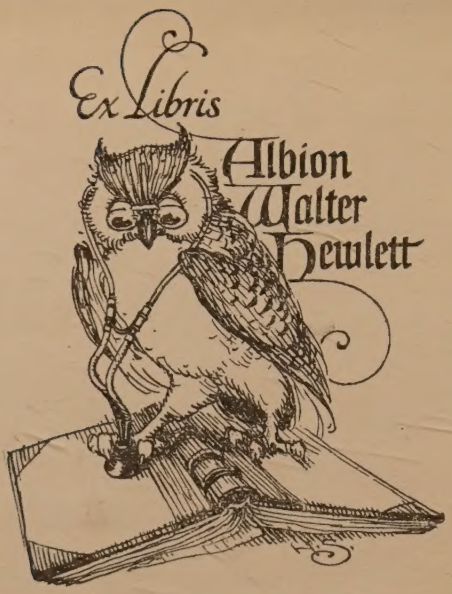

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ENDOCRINOLOGY AND METABOLISM

PRESENTED IN THEIR SCIENTIFIC AND PRACTICAL CLINICAL ASPECTS BY NINETY-EIGHT CONTRIBUTORS

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VOLUME 1

D. APPLETON AND COMPANY

NEW YORK LONDON

1922

MP

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EDITOR'S PREFATORY NOTE

On writing the chapters upon metabolism and the internal secretions for my "Clinical Diagnosis of Internal Diseases" I was impressed with the need for a treatise that would deal with these subjects in a more comprehensive way. Many important monographs bearing upon one or another topic in the field have appeared in this and other countries. Periodical medical literature contains an ever-increasing number of observations and researches bearing upon disorders of metabolism and upon diseases in which the functions and structure of the ductless glands are altered. Medical men everywhere are evincing a lively interest in both the practical and the theoretical aspects of these subjects. The time seemed ripe, accordingly, for the publication of a work that would bring together, as far as possible, in reasonable compass, convenient for perusal and reference, all the essential facts that bear upon metabolism and the internal secretions in health and in disease.

The editor and the associate editors, in drawing up the plan for the four volumes, have kept in mind the desirability of presenting in something like adequate measure and proportion the various materials—anatomical, physiological, chemical, experimental pathological and clinical—that bear upon the endocrine glands and their functions and upon the processes of metabolism. In their division and apportionment of the subjects they have tried to strike a happy mean between overexpansion, on the one hand, and a futile brevity on the other. It seemed to them important to have the subjects dealt with in a manner suited to the needs of practitioners of medicine as well as of original workers in these special fields and not merely to produce a short textbook adapted only to the means and minds of the younger medical students.

Mention of the chief distinctive features of these volumes will give the reader an idea of the service that has been attempted. These features include:

1. Concise, authoritative statements of knowledge and opinion as it exists at the time of writing regarding the internal secretions and metabolism in health and in disease.

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2. A treatise systematically planned by the editors but composed with the collaboration of a large body of scholars, including both clinical and laboratory workers from different sections of the United States and Canada.

3. Especial attention to the needs of the general practitioner while at the same time supplying the scientific foundation for clinical work and data indispensable to laboratory workers investigating metabolic and endocrine domains.

4. A selected bibliography that will permit any reader easily to consult the original articles that are the sources of existent knowledge.

The editor and his associates have been much gratified by the ready and hearty coöperation of the distinguished body of contributors who have composed the work. The energy and enthusiasm of these writers has done much to lighten the labors of both editors and publishers and to assure them of the timeliness of the project.

At a time like this when the cost of paper and of printing is almost prohibitive it would seem essential that the contents of books that are published should be correspondingly more valuable. This is no time for indiscriminate publication of cursory observations or untested ideas. On the contrary, publication should be strictly limited to concise and accurate presentations of the most important subjects. So much speculative nonsense has been written of late upon metabolic and especially upon endocrine topics that there is great need for critical sifting and for conservative pronouncements of judgment by competent workers in order that fields that should be fair may be kept free of weeds.

It was our intention, at first, to append to each single article a selected list of references to the bibliography, a method that undoubtedly adds value to the article and permits its writer clearly to indicate sources other than his own work. It was soon found, however, that this method would involve such a vast amount of repetition of references as unduly to expand the space that could be allotted to bibliography. At the risk of doing violence to the value of the single articles, and against the protest of a few of our most valued contributors who feared that the omission of specific reference numerals by which the authority for certain statements could be readily identified might lay them open to the charge of failure to give due credit to other workers, it was decided that, on the whole, the interests of readers would be best served by publishing all the bibliographic references, arranged in groups, in a separate volume. Objections can be raised to

either method of procedure, but both editors and publishers believe that their decision will be generally sanctioned.

As the preparation of the work has progressed it has become clear that we have been engaged upon an important and rewarding enterprise. The volumes include the results of researches on metabolism and internal secretions in all countries. No attempt has been made to magnify the achievements of our own country at the expense of others. On the contrary, the effort has been made to do justice to the workers in these fields among all the nations of the world.

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SECTION I

General Considerations Regarding Endocrinology

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Nomenclature—The Endocrin Literature—Nature of the Internal Secretions—Conditions Determining Internal Secretions—Methods by Which Endocrin Functions Are Mediated—Evolution of Hormone Control—Duality of the Endocrin Organs—The Endocrin Organs and Old Age—Endocrin Factors Determining Racial and Individual Characteristics—Methods of Investigation of Endocrin Functions—Conclusion.

Introduction

R. G. HOSKINS

COLUMBUS

The basic idea upon which the modern endocrin doctrine is founded is an old one. That each organ of the body contributes a characteristic substance to the blood has been believed more or less explicitly for centuries. A crude form of the idea is the belief, held by various primitive peoples, that in each organ resides some peculiar virtue and this virtue is transferred to any one who consumes the organ. Another less naïve aspect of the same view has long persisted as a belief that diseases of one sort or another are due to deficiencies in the peculiar substances derived from different organs. In accordance with this conception the disease must be treated by supplying the deficient substance. This method of therapy was practiced in the time of Hippocrates. It was favored by Celsus and Dioscorides. Wolf's liver, for instance, was used for hepatic disease, hare's brain for tumors, fox lungs for dyspnea, and ox eyes for iritis. Pliny advised the use of testicular material of donkeys and stags as aphrodisiacs. The system of therapeutics of which these examples form the crude beginning is known as opotherapy. It is only of recent years, however, that the system has had any fruitful developments, as in the use of thyroid extract in cases of cretinism. The history of the gradual evolution of the endocrin doctrine is treated at length in a subsequent chapter.

That every cell contributes to the common circulating medium cannot be doubted. The life processes of each depend upon intricate chemical reactions, the end products of which, the metabolites so-called, are constantly being discharged into the blood, either directly or by way of the lymph stream. In addition to the metabolites, however, which are more or less common to the living cells in general, certain of the body tissues give off more specific products, such as the epinephrin of the suprarenal glands. These substances are known as the *internal secretions*. The term was proposed originally by Claude Bernard to designate the dextrose discharged from the liver, in contradistinction to bile, the secretion proper. Such substances as dextrose, however, are not included in the modern conception of the term.

Nomenclature

A fairly complex terminology has been developed in the field of endocrinology and one which, to the casual reader, is likely to give a false sense of security regarding the fundamental data to which it pertains. That the nomenclature has become relatively overextensive has been deplored by Gley and others.

Until recently the structures that produce internal secretions have been known as the *ductless glands,*—a term that still has some currency. In certain instances the term is apt but it is unsatisfactory in that it excludes certain of the glands with ducts, organs that produce internal as well as their better known external secretions. An example of these is the pancreas. Recently the term *endocrin glands* has come into general use to designate all structures having, or supposed to have, an internal secretion. These comprise the pineal, pituitary, thyroid, thymus, suprarenal, pancreatic and sex glands and, less definitely, the salivary glands, spleen, kidneys and intestines, and, possibly, the liver. The "glandula insularis" of Pende and the "myometrial gland" of the uterus are possibly endocrin structures also.

In a sense, all the various metabolites of the body are "internal secretions." But as a more specific appellation to designate the products of the endocrin tissues, Bayliss and Starling have proposed the term *"hormone,"* a word derived from the Greek ὅρμαω, meaning "I excite." A hormone is defined as a substance produced in one part of the body and carried by the blood or lymph to some other part, the activity of which is thereby modified. As characterizing the internal secretions that affect more particularly the growth and developmental processes Gley has introduced the term "harmozones," from ἁρμόζω, I rule or direct.

Although the term hormone itself has come into very general use, even among the laity, it has little more than usage to commend it. By definition the term means an excitor, but various hormones, as a matter of fact, actually depress bodily functions.

In view of this fact Schafer has proposed a different terminology. Instead of hormones he suggests that the specific internal secretions be called "autocoid substances," or "autocoids" (from αὐτός, self, and ἄκος, a drug or remedy). The autocoids comprise two classes,—"hormones," which excite functions, and "chalones," which depress. That the situation would be improved by the adoption of these terms seems doubtful. The word hormone would at once come to have an ambiguous significance, depending on whether the newer or older usage were understood. Moreover, the word autocoid is hardly a happy selection. The word drug connotes a foreign substance, whereas internal secretions are precisely the

opposite. Neither is it feasible, as Schafer himself points out, to classify internal secretions as exciting or depressing. Epinephrin, regarded by many as the best known of the hormones, excites some tissues and depresses others. For example, in small quantities, it causes the blood vessels of the skin to constrict, while those of the underlying muscles dilate. Moreover, the effect of epinephrin in certain tissues may be either excitation or depression, depending upon the amount used. Thus, although moderate concentration of this substance passed through the blood vessels of skeletal muscles cause augmented venous outflow, larger quantities result in a diminished flow. A similar reversal of effect with change of dosage, has been reported in the lungs.

The attempt to meet the difficulty by the assumption that the process is actually excitation in each instance,—in the one case augmenting, and in the other depressing mechanisms being involved,—will scarcely appeal to the thoughtful reader. It merely raises the much debated question as to the nature of inhibition. If, as Verworn has maintained, inhibition amounts merely to continuous subminimal stimulation, there would be no need for the word chalone.

Similar criticisms are to be offered against Biedl's division of all internal secretions into "erregende" and "hemmende," i. e., exciting and depressing. The same may be said of Livon's division of the hormones into "hypertensive" and "hypotensive." Under different conditions the same substance, for example, epinephrin, may be either exciting or depressing, hypertensive or hypotensive.

As descriptive of the tissues producing internal secretions, Matthews has used the word "cryptorrhetic," meaning "with a hidden flow." Since the term has the same practical significance as the better known "endocrin," it would seem that its adoption would merely serve further to complicate the situation without improving it.

Among certain American writers the term "endocrines" has come into a certain vogue as a generic appellation to include all the organs of internal secretion. Etymologically the term is not a happy one, being an adjective made to serve as a noun, just as "humans" is sometimes carelessly used as a synonym for "human beings." It is to be hoped that the term will be discarded.

Similar carelessness as regards linguistic niceties has resulted in the introduction of such Greek-Latin hybrids as "adrenalemia," "suprarenalemia," and "adrenalectomy." "Epinephrinemia" and "epinephrectomy" are scarcely more formidable and are etymologically much to be preferred.

The terminology as regards specific internal secretions is somewhat redundant. For the suprarenal hormone we have epinephrin, a term first applied by Abel, though to a benzoyle addition product rather than to the specific principle itself. Among more punctilious American

writers this term is most often employed. By others, however, it is little used. The term adrenalin has come into most common use in the scientific world at large, despite its having been adopted by a pharmaceutical house as a trade name. Adrenin, which would seem to be most satisfactory in point of simplicity, has had a certain vogue among British and American writers, but seems to be employed less frequently now than formerly. A fuller discussion of the terminology on this point will be found in the chapter on the biochemistry of the suprarenals.

As regards generic terms for other endocrin substances, there is little uniformity, and little is to be expected until the individual hormones are isolated and chemically identified. Thyroxin has recently been introduced by Kendall as a term to designate the active principle of the thyroid gland. He has claimed—and the claim is being gradually recognized—that this substance is the actual thyroid hormone. Other terms for this are discussed in the chapter on the chemistry of the thyroid. The pharmacologically active constituents of hypophyseal extracts are fairly generally known as pituitrin and hypophysin, but there is no definitely accepted usage on the point. Final adoption of a satisfactory term will probably wait upon the actual isolation of the substance or substances; these the discoverer will have the right to christen as he sees fit. For many years spermin has been in use as vaguely indicating the hormone of the testis. Although the substance is recognized as a definite nitrogenous body, there is little reason to suppose that it represents the true internal secretion of the gonads. Numerous other terms are in use as designating assumed "active principles" of the various endocrin organs. For the most part the meaning of the terms is obvious. Until the bodies referred to are actually isolated and chemically identified the terminology in such cases is necessarily provisional.

The Endocrin Literature

To the physician or biologist who has not had occasion to make a special study of it, the magnitude of the present-day literature on the glands of internal secretion is probably not suspected. Interest in the subject extends through all fields of animal biology, as well as to all branches of clinical medicine. At the present day important contributions are appearing in a dozen languages in hundreds of different medical and scientific journals and books.

Until about 1890 relatively few articles of interest in this field had been published. A great stimulus to the study of the glands of internal secretion was afforded by the epoch-making work of Brown-Séquard on testicular extracts. Although the work in itself ultimately came to be regarded as of dubious immediate significance, it aroused world-wide in-

terest in the possibilities of endocrin biology. In 1912 Biedl, in the second edition of his well-known monograph, "Die innere Sekretion," published a systematic compilation of the literature. His bibliography of some 212 pages included about seven thousand articles which dealt directly with the endocrin glands. The rapid growth of the literature at this time is evidenced by the fact that after the manuscript was submitted to the printer and before the book was through the press some fifteen hundred new articles had appeared, necessitating the addition of 41 supplementary pages of bibliography. This brought the literature up to 1913. There were then approximately 8500 titles in Biedl's list. There is no available record of the number of papers appearing during the period from 1913 to 1916, but, judging by the number of articles preceding and following this period, four thousand might be regarded as a safe estimate. During the period of the war the output in this field was of course restricted, but even during this time several hundred articles appeared each year. Since the war the output has again increased. At the present time the journal *Endocrinology,* which attempts to list all original articles in the field, is publishing about fifteen hundred titles a year.

Nature of the Internal Secretions

As an example of a typical hormone "secretin" may serve. This is a substance formed in the mucous wall of the duodenum by the action of the chyme on an antecedent "prosecretin." The secretin is absorbed into the blood and carried to the cells of the pancreas and perhaps the liver, and these organs are thereby excited to secretory activity. Possibly a more striking example was afforded a few years since by the so-called "Bohemian twins," the Blazek sisters of Continental museum fame, whose case was reported by Trunecek (1910). The bodies of these women were united along one side, i.e., they constituted a living pygopagus monster, so that while they were otherwise independent organisms, the blood stream was in a measure common to both. When one of the twins became pregnant the mammary glands of each hypertrophied, and after the infant was born each was able to nourish it. The most plausible explanation for the phenomenon is that during the development of the fetus something was contributed to the common blood stream which stimulated the mammary tissues of both women.

Such examples of bodily reactions to circulating chemical substances are by no means unique, nor are the endocrin glands the only source of such active materials. One of the most important regulatory substances of this kind is carbon dioxid. This gas is formed as an end product of oxidation in all the cells of the body, but particularly in the muscles. Whenever the muscular activity is increased the carbon dioxid concen-

tration of the blood is raised. The respiratory center is thereby stimulated and the breathing movements become more rapid and deep. Thus more oxygen is supplied and the carbon dioxid more rapidly excreted. Respiration is then carried on at this increased level as long as the increased muscular activity persists and automatically decreases when the activity lessens and thus lowers the rate of carbon dioxid production.

The stimulating effect of carbon dioxid is due to the fact that it unites with water to form an acid. There are other acid fatigue products that have a similar influence. Nor is the respiratory center the only structure which reacts to such acid products. The activity of the heart also is increased and the laboring muscles thereby supplied with more blood. A similar adaptive result is attained by local dilatation of the capillaries of the active tissues. These reactions are among the most important adaptations with which biologists are familiar. For nonspecific regulatory substances such as carbon dioxid, Gley has proposed the designation *"parhormones."*

The internal secretions are entirely different in nature from the ordinary secretory products of gland-cell activity, such as saliva, or the excretions, such as urine. The ordinary secretions are characterized by their ferment or enzyme constituents. Through much study these have become fairly well known. They exist not only in the external output from various cells, but also in the cells themselves and in the circulating fluids. The enzymes are apparently complex in their chemical structure; they are probably proteins. They are sensitive to the presence of hydrogen ions and have an optimum temperature at which they function best. In the presence of water they are readily destroyed by heat and by digestion. They are specifically adapted to the substrates upon which they act.

The hormones, on the other hand, are, so far as known, much simpler bodies. They are crystallizable and dialyze freely. They withstand boiling and, according to Abderhalden, are not destroyed by the action of the digestive juices. Some of them, such as epinephrin, act much more rapidly than do the enzymes, but others, acting as they do upon the developmental processes, show their influence only after a prolonged period. A hormone from the suprarenal glands, epinephrin, has been isolated in a pure form. That the active principles of the thyroid, hypophysis, and testes have been similarly isolated has also been claimed. Epinephrin and thyroxin have been artificially synthesized. Doubtless as their chemical nature becomes better known, other hormones will be similarly produced. None of the internal secretions, so far as we know at present, gives rise to anti-body formation. The individual hormones apparently do not differ among the various species of animals; that is, they show physiologic but not zoölogic specificity. Epinephrin, for ex-

ample, has identical properties whether derived from the sheep or the whale. A striking feature in case of some of these substances is their high potency. Epinephrin has been shown to exercise a perceptible effect on smooth muscle in dilution of one part in a billion, or about one grain in fifty tons of fluid. The presence of one part in ten millions is easily detected by several of the more delicate biologic methods. Another striking characteristic of epinephrin is its instability. Even a relatively large dose administered intravenously to an animal seems to be quickly destroyed, although Meltzer and Auer have shown that when injected subcutaneously it may cause local vascular changes that persist for hours. If the substance is injected directly into an artery it is so nearly completely removed during its passage through the capillary bed as to exert no demonstrable systemic effect unless relatively very large doses are employed. The thyroid hormone, on the other hand, appears to be relatively stable, continuing to exert its effect, for example, on basal metabolism for days (Plummer).

The internal secretions proper are to be differentiated from other specific substances found in the blood, such as those involved in the processes of coagulation or in immunity. In some instances the grounds for division are not at all definite. The opsonins, for instance, are "derived from cells in one part of the body and influence functions elsewhere," and thus fall within the conventional definition of hormones. Properly speaking, however, they are not such. Until our knowledge of the chemistry of both immunity and endocrin biology is better established the classification in such cases must be somewhat arbitrary.

In considering the active principles of the endocrin glands the fact should not be ignored that the discovery of one such principle in a given organ by no means excludes the possibility of the existence of others. That the suprarenal and pituitary organs produce more than one active substance each is highly probable. The corpus luteum is generally believed to produce a hormone different from any formed by the ovary proper.

In the therapeutic use of endocrin material these facts should be held in mind. That suprarenal therapy now has questionable standing is possibly due to some extent to a premature conclusion that epinephrin is *the* active principle rather than *an* active principle of the gland. Negative results with epinephrin by no means prove that suprarenal treatment is necessarily without value. Unfortunate is the assumption on the part of pharmaceutical manufacturers that any process, which does not destroy a recognized "principle," may safely be used in preparing gland extracts or desiccated gland substances for clinical use. The custom of extracting these materials with fat solvents undoubtedly makes for elegance in the finished products but it may also, in some cases, account for the uselessness of the same.

Conditions Determining Internal Secretions

In a classical treatise with which all students of endocrin science should be familiar, Gley (1917) has considered at length the conditions that determine whether or no any given organ can logically be included in the endocrin congeries.

Three conditions, while they suffice, must all be met before any given structure can be placed definitely among the organs of internal secretion. The determining conditions are, respectively, histological, chemical and physiological. The cells of the organ or tissue in question must show evidence of secretory function, such as the presence of granular precursors or mitochondria and the cells must exhibit a polarity in relation to the excretory channels, the efferent vessels. Second, it is necessary to demonstrate the presence of a peculiar chemical entity both in the cells and the efferent blood or lymph. Finally, the blood or lymph must be shown to exhibit pharmacodynamic or growth influencing properties not demonstrable, or demonstrable only to much less extent in the blood or lymph of the body in general.

As a matter of fact, these conditions have not all been met in various organs conventionally included among the endocrin glands. In case of even the thyroid many attempts to meet the third criterion have been unsuccessful. Of recent years, however, researches in Asher's and Cannon's laboratories have perhaps satisfied the requirement by showing that the reactions to epinephrin are distinctly modified by stimulation of the nerves to the thyroid gland. In any case, however, the effects of thyroid extirpation are so clean cut and characteristic, and the effects of thyroid extract in alleviating the symptoms of thyroid deficiency are so well marked that no reasonable doubt can be entertained that this gland has an endocrin function.

Histological Condition.—The endocrin organs proper are without ducts leading to the exterior and this is also true of the endocrin tissues that are incorporated in the pancreas and the gonads. These structures are permeated by a rich supply of blood vessels with which their cellular elements are in intimate connection, toward which they are polarized, and into which their secretions are discharged. Regarding such a structure as the pancreas or the liver, organs which are provided with ducts for external discharge of their secretions but which also discharge directly into the blood stream, a double polarity is manifested. Similarly in the duodenojejunal mucous membrane this dual polarity is seen. The cells discharge their digestive secretions into the intestinal cavity, but they also deliver to the blood a substance, secretin, which serves as a hormone for the pancreas. The processes of digestion and absorption in the alimentary tract afford various other examples of cell layers which discharge

in opposite directions. Such physiologic bipolarity of the cell is associated with a morphologic bipolarity in that special activity may be demonstrated in the opposite zones of the cell. Thus mitochondria may be demonstrated in both the supranuclear and infranuclear zones, whereas in the ordinary secreting cell one zone only is seen. Hence from a mere study of the microscopic picture of the individual cell, to determine whether it is oriented as regards nucleus and granular inclusions toward ducts or toward the capillaries, it is often possible to decide whether the structure has an ordinary external secretion or an internal secretion proper. In general, then, it may be stated as a necessary condition before a structure can be regarded as having an endocrin function that it must be made up of cellular elements, that the cells show morphologic evidence of secretory activity, and that the cells have a definite orientation toward the blood or lymph channels.

Chemical Condition.—Every product of secretion, external or internal, is the result of chemical processes within the cells. The product must be recognizable by its chemical characteristics and be identified as an entity, both in the cell itself and in the efferent vessels. In only a few instances have the characteristic products of the endocrin tissues been thus demonstrated within the cells. That epinephrin so exists in the suprarenal medulla has been proved. In the thyroid cells also a characteristic colloid is found and this has been demonstrated in the efferent vessels. The relation of this colloid, however, to the hormone proper has not been definitely determined. In case of the other endocrin organs little progress has as yet been made in satisfying the logical requirement postulated in the caption of this paragraph.

Physiological Condition.—Fulfillment of this third condition, as previously stated, requires the demonstration of a specific substance in the efferent vessels by means of various physiological reactions when blood or lymph is injected into a second animal. Obviously, to permit such demonstration the substance in question must maintain its identity in the blood stream long enough to permit it to reach the capillary circulation of the effector mechanisms through which the activity is manifested. The dilution factor may interpose a serious difficulty. In the case of epinephrin the substance can be obtained in sufficient concentration in the lumbo-adrenal veins to permit the demonstration of its presence by several methods. Even when it is diluted by the total blood volume of the recipient test animal, pharmacodynamic effects can be seen in a number of different organs.

Observations made in Cushing's laboratory have been widely quoted as showing the possibility of demonstrating the active principle of the pituitary organ in the cerebrospinal fluid into which it has been supposed to be discharged. Recently, however, upon careful restudy of the problem, Jacobson, one of the original observers, has reached the conclusion that

the demonstration of the substance as claimed cannot be made with technique at present available.

Such failure to demonstrate the presence of a specific secretion does not, as a matter of fact, carry much conviction of its absence. In the normal animal a very minute quantity of a given hormone may exercise a cumulative effect extending over days or weeks, thus functioning in a way that could not be detected in a short-lasting experiment. To demonstrate such a cumulative effect would not be practicable ordinarily, because it would necessitate the administration of too great a quantity of foreign blood to an experimental animal, thus introducing an uncontrollable variable. The obvious method of meeting the difficulty would be to obtain the substance in question from the blood or lymph and then to concentrate it to an extent that would permit its study by the ordinary pharmacologic or animal feeding technique. The evolution of methods for obtaining and concentrating the various undetermined hormones will in all probability await the determination of their chemical properties.

Many attempts to determine indirectly the presence of essential hormones in the blood coming from different endocrin organs have been made. The efferent veins have been ligated and the resulting functional perturbations studied. These manifestations can, with some degree of probability, be regarded as due to deficiencies of the hormones in question. Hartman, for instance, has recently applied this method to the suprarenals. He found that when the lumbo-adrenal veins were ligated at the proximal side of the glands sufficient circulation was maintained through collateral vessels to prevent absolute destruction of the glands and the consequent death of the experimental animal. The procedure did result, however, in a number of interesting phenomena. These are to be further studied.

Perhaps the earliest attempt to utilize the method was made by Gley in 1891. This observer noted that ligation of the pancreatic veins resulted in glycosuria. The experimental animal soon died, however, thus forestalling any extensive study of the results of the experiment. Minkowski's well-known experiments on pancreatic extirpation have often been cited as bearing upon the point at issue. If the pancreas be removed in toto the animal soon dies of acute diabetes. But if a portion of the gland be transplanted, preserving the circulation intact but occluding the excretory duct, the animal survives. Forsbach's modification of the experiment may also be mentioned. The bodies of two dogs were surgically united so as to produce parabiotic "twins." Removal of the pancreas of one resulted in but slight glycosuria instead of the fatal diabetes which would otherwise have followed. Another variant of the procedure is the crossed circulation experiment of Hédon. This investigator noted that when the blood streams of a diabetic and a normal dog were united by anastomosing an artery and vein of one to a vein and an artery of the other, the glycosuria in the diabetic animal was materially reduced. Such experiments,

however, are not conclusive. The glycosuria and other diabetic symptoms that result from the extirpation of the pancreas might be due to the accumulation of toxins or metabolites in the blood, which, in the normal animal, are removed or destroyed by the pancreas. This objection, however, cannot be offered to the observations of Hédon and of Carlson, that transfusion of blood from the pancreatic vein of a normal animal into the general circulation of a diabetic results in a diminution of the glycosuria characteristic of the condition. On the other hand, the objection has been offered that such reduction might be due merely to ill-defined "depressive" action of the foreign blood.

One of the most satisfactory demonstrations of the presence of a hormone in efferent blood may be obtained by the so-called "crucial test" of the production of secretin when acid is placed in the duodenum and the duodenal venous blood shunted directly to the denervated pancreas. The prompt appearance of augmented secretion in that gland would seem to constitute indubitable proof of the presence of secretin in the blood.

Another indirect physiological proof of the existence of a hormone in the blood has been stressed by Gley (1917). This is the observation recorded by Miranoff that the denervated mammary glands of a female goat hypertrophied during pregnancy and later secreted in a normal way. Similarly, transplanted mammary glands have been shown to go through the normal hypertrophic and secretory cycle during and following pregnancy. Such glands are supposedly free from the influence of any normal nerve impulses and are hence amenable only to chemical influences.

Such experiments are obviously open to the same objection as was mentioned in the case of the pancreas. The hyperplasia may conceivably be due merely to removal from the blood stream of some inhibitory substance which, in the non-pregnant state, holds the mammary tissues in an inactive condition. Granting the existence of the assumed hormone leading to mammary hyperplasia, its source remains still unknown. It has been ascribed by various investigators to the placenta and by others to the fetus in utero. Support is lent to the latter hypothesis by the experiments of Lane-Clapon and Starling and of Foà. These observers noted mammary hyperplasia following injections of extracts of macerated fetuses. Frank, however, has failed to confirm the observations and has stressed the difficulty inherent in the marked variability of the normal mammary glands, even in virgin animals.

Other data bearing upon the topic under discussion will be found in subsequent paragraphs under the caption "Methods of Experimentation." At this point, however, it should be emphasized that despite a vast amount of experimentation, we are still much farther from a logical proof of the existence of numerous assumed hormones than is generally recognized. In case of the thyroid and suprarenal glands only have Gley's three conditions been met. Moreover, even in case of the suprarenal, concerning

which our knowledge is most extensive, doubt is entertained by such able physiologists as Gley and Carlson that epinephrin exercises a true hormone function. The possibility remains open that this substance, which may be demonstrated in the gland and which under artificial conditions can be demonstrated in the efferent blood vessels, is merely an intermediary product of metabolism—that under normal conditions epinephrin is not discharged as such at all, but is further elaborated into an inert body before it reaches the blood stream. A close analogy to this assumed condition exists in case of urea, which is a harmless end product of potentially harmful nitrogenous metabolites, formed, in part at least, in the liver and discharged via the blood stream through the kidneys.

Methods by Which Endocrin Functions Are Mediated

In the present state of our knowledge an adequate discussion of the methods by which the endocrin glands produce their effects is impossible. Indeed, the very term endocrin, as applied to more than one gland, may be entirely a misnomer. We are wont to assume that any organ which produces effects at a distance without the intervention of the nervous system does so by contributing a specific substance to the circulating medium. But in various instances, as previously stated, the effects may equally well be explained by an assumption that active substances are removed from the blood and converted into inactive forms as, for example, ammonium salts are converted to urea. Since the discovery of the potency of certain gland extracts, this possibility has largely been ignored. It may well be that future researches will show it to be deserving of more consideration. For a long time the most probable function assigned to the "ductless glands" was that of "detoxicating" the blood. The symptoms that arise after the removal of the parathyroid glands suggest a failure of some detoxicating mechanism. As able a physiologist as Luciani believed that the effects of suprarenal extirpation are likewise due to the accumulation of toxins that are normally removed and destroyed by these glands. As against this hypothesis may be urged the fact that from the body of no animal dying after suprarenal extirpation has a definite toxin been isolated. The writer some years since studied at some length the influence of the blood of dogs dying or recently dead of suprarenal failure on cardiac or skeletal muscular function. No difference could be detected in the activity of the isolated heart beating in normal dog's blood from that of a similar preparation in the blood of an animal from which the suprarenal glands had been removed. Similarly it was found that the activity of a stimulated gastrocnemius was equally extensive and prolonged in either sort of blood. These test tissues were selected because of the fact that cardiac and skeletal muscular weakness are the outstanding features

resulting from suprarenal insufficiency. The experiments, however, did not exclude the possibility that in the condition mentioned a slow acting toxin might conceivably accumulate and thus cause the symptoms of suprarenal deficiency. The possibility remains open, not only as regards the suprarenals, but also as regards various other organs that their extirpation may lead to a gradual intoxication which might materially influence growth and the various functional processes. Likewise, a gland of the "endocrin" congeries might remove from the blood stream certain substances which normally hold in check a tendency to overgrowth of some of the tissues. The increased size of castrated cockerels, that is capons, might well be due to such a cause.

Other possibilities present themselves. The endocrin glands may contribute to the blood stream bodies in the nature of amboceptors whereby the tissue cells are enabled to assimilate different substances necessary for their normal metabolism. Such a conception fits in fairly well with what is known regarding the endocrin function of the pancreas. The internal secretions may in some cases serve as catalyzers to facilitate the specific chemical processes in the various body cells. Such an assumption has been made by Plummer, and with much plausibility, in the case of the thyroid secretion. Allen has gone so far as to suggest that certain of the endocrin activities may even be dependent upon the manifestation of some sort of energy of a nature as yet entirely unsuspected, as was the action of radium a generation ago.

In some instances the effects of administering endocrin gland substances by grafting or otherwise seem to be due, in part at least, to the stimulation of latent cells of the corresponding organs. For example, a case has been described by Morris (1916) in which a testicular graft was implanted to compensate for atrophy of the gonads. The procedure resulted in a marked development of the atrophic testes which had been left in situ. Similarly, the use of thyroid material is said to stimulate the thyroid glands. This assumption is sometimes referred to as "Hallion's law." Indeed, some authors have even gone so far as to maintain that the only way an endocrin product can produce significant therapeutic effects in the body is by stimulating tissues similar to those from which the product is derived. The "law," however, has not generally been admitted as valid.

The major problem as regards the mediation of hormone influences is, whether the body cells are affected directly or through the nervous system, or in both ways simultaneously. In case of epinephrin there is abundant evidence that the striking pharmacodynamic effects following its injection are due to selective stimulation of the sympathetic nervous system. The stimulation affects largely the neural terminals or, more specifically, the neurocellular junctional material, the "receptive substance" of Langley. Thus in organs supplied with stimulating sympathetic fibers epinephrin

augments activity, as in case of the heart; whereas in organs deriving their inhibitory innervation from the sympathetic system the effect is depression of function, as in the gastro-intestinal tract. That the pharmacodynamic effects of epinephrin are not due solely to peripheral action, however, has recently been shown by Hartman and his collaborators. These observers have noted that various of the reactions, and especially vasodilatation, can be evoked by the application of epinephrin to the sympathetic ganglia.

That the well-known pharmacodynamic effects that follow the injection of epinephrin represent merely an exaggeration of the normal functions of the suprarenals has been widely assumed. The assumption is still made the basis for a considerable amount of clinical theorizing. A consideration of the quantitative factors, however, renders this very dubious. No reliable evidence has ever been reported that epinephrin can be found under normal conditions in the arterial blood in sufficient concentration to bring about such functional perturbations as rise of blood pressure, glycosuria, and the other well-known reactions to large doses of the drug. The most recent investigations, in which the best available technique has been employed, have indicated an output of epinephrin from the suprarenal glands of only approximately 0.0002 milligram per kilogram of body weight per minute, and this output has been obtained under conditions of trauma and anesthesia that in all probability markedly augment the discharge.

That the sympathetic nervous system is under constant minimal epinephrin stimulation is the basis of the so-called tonus theory of suprarenal function. Following Oliver and Schäfer's classic experiments with suprarenal extracts, the tonus theory was propounded and widely adopted. A number of observations, however, render the theory highly dubious or, indeed, in the opinion of many competent investigators, quite untenable. The theory has been applied more particularly to the control of blood pressure. It assumes that the suprarenals are constantly supplying to the blood stream enough secretion to stimulate the pressor mechanisms. If this were true the addition of a slightly greater quantity of the drug by vein should augment the pressor influence and send the tension higher. As a matter of fact, quite the opposite occurs. Such injections characteristically lower the blood pressure. This observation was made by Moore and Purinton as early as 1900, but the depression was ascribed to impurities in the material injected. In 1912 Hoskins and McClure reinvestigated the matter, using a supposedly pure drug. Their experiments were made on dogs. The depressor effect was easily demonstrated. In one striking instance, by the infusion into a vein of a dilute solution of epinephrin, the blood pressure was reduced by several millimeters and held at this lower level for ten minutes until the infusion was discontinued, when the pressure promptly returned to its former height. The depressor effect of small doses was confirmed by Cannon and Lyman

in cats. In 1913 Hoskins and McPeek showed that light massage of the suprarenal glands leads to a similar fall of blood pressure.

Again, if the suprarenals normally pour into the blood stream enough secretion to maintain a significant augmentation of pressure, sudden occlusion of the suprarenal veins should result in a prompt depressor effect. This follows from the fact that epinephrin is quickly removed during the passage of the blood through the capillary bed. As a matter of fact, such occlusion characteristically leaves the pressure precisely where it was before. The depression which ultimately appears occurs only after a matter of hours or in some cases even of days.

Hoskins and McClure tested the theory in another way. If dilute epinephrin be injected into a vein at a very slow but gradually increasing rate, at first no effect at all is seen. Then various changes occur. The earliest of these is depression of intestinal peristalsis. If simultaneous records of peristalsis and blood pressure are taken it is found that the gut is paralyzed before any rise of blood pressure occurs. One need scarcely point out the unliklihood that blood pressure is normally maintained by any mechanism that involves gastro-intestinal paralysis. Among physiologists the tonus theory has on such grounds largely been discarded; but among clinicians it is still occasionally invoked to account for various symptoms.

But the fact remains that suprarenal extirpation leads to death and the final symptoms include a failure of functions that are under sympathetic control. Elliott (1905) has offered the interesting suggestion that a minute quantity of circulating epinephrin is necessary, not to stimulate the sympathetic system, but to maintain its irritability; that in its absence the terminal neurocellular substance of the sympathetic system is no longer able to transmit impulses. This possibility also was investigated in the writer's laboratory. It seemed that animals at the point of death, such as Elliott studied, should not be deemed capable of giving any very significant information. All sorts of secondary factors might have entered into the experiment. If sympathetic failure is a characteristic feature of the syndrome, it should appear at an early stage. Experimentally it was found that at a time when the animal deprived of its suprarenals, was showing marked symptoms, when it could scarcely sustain its own weight, its vasomotor system responded to stimulation perfectly well. The observation was repeated upon numerous animals. Hence sympathetic failure following suprarenal extirpation is to be regarded as a secondary feature. Both cardiac and muscular weakness precede it. It would seem probable that if, as Elliott supposed, a trace of epinephrin is essential for sympathetic function, the vasomotor reaction should be improved if an animal previously deprived of its suprarenals were to receive a continuous injection of very dilute epinephrin for such a period, for instance, as half an hour. By direct experiment the surprising fact was discovered

that such injections often materially impede sympathetic function. In some cases well marked block of sympathetic conduction was demonstrated. This observation, which was confirmed many times both in normal animals and those deprived of their suprarenals, seems to disprove the alternative theory that epinephrin normally facilitates sympathetic function.

So much for experiments of negative tenor. Boothby has recently reported that as little as 0.5 milligram of epinephrin administered hypodermatically may evoke a very marked augmentation of basal metabolism in an adult human being. The effect persists for a matter of hours. At no time under the conditions of the experiment could more than an almost infinitesimal amount of the epinephrin injected be present in the blood stream—a quantity much less than that employed in classic pharmacologic experiments. The sum total of available present-day evidence seems to indicate that epinephrin, in the very small quantities which are probably not transcended under normal conditions, influences in some way the metabolic processes leading to the acceleration of the oxidation reactions directly. A variant of this assumption has been developed at length by Sajous in his "respiration theory" of suprarenal function. This writer believes that epinephrin plays a significant rôle in the taking up of oxygen from the lungs and facilitates its use by the tissues. Further data on the significance of epinephrin in relation to body function are included in the chapter on "The Pharmacology of the Suprarenals."

In case of hypophyseal extracts, many of the pharmacodynamic effects, at least, are due to stimulation of the smooth muscle throughout the body, irrespective of its innervation. In many organs the effects are similar to those of epinephrin, as for example, in the heart. In case of the intestine, however, whereas epinephrin causes inhibition of peristalsis hypophyseal extracts give predominantly a stimulating effect. That such extracts, however, exert their influence through the nervous system is believed by some observers. Further details will be found in the chapter on "The Pharmacology of the Hypophysis."

The thyroid hormone seems to have a twofold effect, both catalyzing the metabolism of effector cells directly and augmenting the irritability of the nervous system. This augmenting effect is particularly well seen in the sympathetic system. It is upon the sensitization of the sympathetic system that the well-known "Goetsch test" for "hyperthyroidism" is based. The topic is further discussed in the chapter on "Tests for Thyroid Disorders."

In addition to the endocrin products above mentioned, which perceptibly influence various functions within a relatively short time after their administration, there are others, the morphogenetic substances, or harmozones of Gley, which manifest their effects only upon the processes of growth and development. The thyroid secretion, in addition to its

immediate effects discussed in the preceding paragraph, has also an important relation to the developmental processes. This is obvious from a comparison of a stunted cretin in whom the thyroid function is suppressed with a normal subject of the same age. The anterior lobe of the hypophysis, the interstitial cells of the gonads, and the corpus luteum also have important morphogenetic functions.

Regarding the details as to how the morphogenetic functions are mediated, we have little clean-cut information. Practically nothing is known as to how deficiency of the hypophysis leads to disproportion of development in the extremities, the skeleton, and the connective tissues; or how the overdevelopment of acromegaly, which is due supposedly to overactivity of the hypophysis, is brought about. That castration results in a prolonged failure of the epiphyses of the bones to close is well known but totally unexplained. We have little definite knowledge as to why thyroid deficiency leads on the one hand to redundancy of subcutaneous material, thus giving rise to myxedema, and on the other hand to arrested development of the skeleton and particularly of the long bones. That the endocrin factors in bone development act in quite different ways is obvious. The hypertrophy seen in acromegaly gives a picture quite unlike the increased growth in the length of bones of castrated subjects.

Other important manifestations of harmozone influences may be seen in the development of the genital tract and its accessory glands. In the male a condition of genital infantilism can be brought about through aplasia of the interstitial cells, the so-called "puberal gland" of the testes, as well as, according to many investigators, perturbed functions of the hypophysis or the pineal gland. Similarly, thyroid deficiency may result in defective development of the genitalia. In the female, normal development of the internal genitalia and of the breasts may be prevented either by thyroid or ovarian deficiency. That various changes in the uterus during the menstrual cycle and numerous bodily changes in pregnancy are due to the corpus luteum or to the interstitial cells of the ovary is highly probable. Ochoterena and Remirez have discussed the evidence on this point.

That some of the morphogenetic factors discussed in the foregoing paragraph may exert their influence through the nervous system is possible. That such changes as mammary hyperplasia, however, can readily be demonstrated after denervation of the gland indicates that in some cases, at any rate, the influence is directly upon the tissue cells.

Regarding the problems of the mediation of hormone control only a beginning has been made. The future will doubtless see developments of the highest importance both to general biology and to clinical medicine. Further data along this line will be found in subsequent chapters on "The Relation of the Endocrin Organs to Growth and Development" and "The Relation of Endocrin Organs to Metabolism."

Evolution of Hormone Control

A consideration of the action of the various hormones suggests an interesting speculation: Have the chemical products been evolved to govern the reactions and growth changes to which they give rise, or have these latter been secondarily evolved in relation to the hormones? The latter is the more probable assumption, and in case of certain of the nonspecific metabolites has been definitely proved. For instance, carbon dioxid production occurs in animals at the very bottom of the scale of life, whereas respiratory movements which are regulated by this compound appear much later. It is not unlikely that in case of the internal secretions, proper, evolution has taken a similar course. Certain body cells we may suppose, in carrying out their peculiar life processes, have come to form unusual products. The body has then developed adaptive reactions to these products. The possibility that epinephrin formation may be merely one phase of a detoxication reaction in relation to which the phenomena postulated in Cannon's "emergency theory" have been secondarily evolved, has been discussed in a preceding paragraph. At any rate, it is true that in certain animals are found substances capable of exerting a marked influence in organs which these particular animals do not possess. Thus it has been found that extracts of the hypophysis of fishes or birds have a marked influence on lactating mammary glands, an influence due apparently to a substance identical with that found in extracts of the hypophyses of mammals, but obviously a galactagogue can be of no use to a fish or a bird.

Starling has suggested the probability that hormone control of body functions was first evolved and that nervous control was later superimposed. In forms even as low as the sponge there are found cells that migrate from one part of the body to another in response to changes in the chemical state of the tissues. In higher animals the migration of leucocytes to a locus of infection is a similar reaction. In favor of Starling's hypothesis may be cited the fact that hormones do affect more particularly the primitive functions, such as growth, digestion, and reproduction.

In case of many bodily activities chemical control would be inadequate. For example, if a missile were rapidly approaching the eye there would be little use in an arrangement whereby some chemical product were discharged into the blood stream and then carried to the muscles to stimulate them to activity. The impending injury would have occurred before any protective reaction could take place. Moreover, the muscles as a whole would be affected rather than those few necessary to avoid the missile. To meet the more sudden vicissitudes of life, therefore, nervous reflex control has been evolved.

Duality of the Endocrin Organs

A striking anatomical peculiarity of several of the organs of internal secretion is their so-called duality. The pituitary body consists of two major distinct structures, the anterior or parenchymal, and the posterior or nervous lobe. Associated with the posterior lobe are the pars intermedia and the pars tuberalis. From the posterior lobe may be derived a potent extract which has a marked effect upon the circulatory apparatus and other parts of the body. Extracts of the anterior lobe, on the other hand, are quite without significant pharmacodynamic effects. The thyroparathyroid apparatus is also composed of two different sorts of tissue, the thyroid gland proper and the parathyroid bodies. In most animals the parathyroids are in close apposition to the thyroid lobes; in some they are imbedded in the thyroid tissue. The suprarenal body in mammals consists of the medulla and, surrounding it, the cortex. From the medulla alone is the active substance epinephrin obtained. Extracts of the cortex, when injected into the blood stream, are without notable effect. In the ovary, at certain periods, is found the corpus luteum, a structure that has an important influence on body functions quite independent of that of the organ in which it is imbedded. The same may be said of the interstitial cells of both the ovary and the testis.

These close anatomical associations are not found, however, in all cases. The parathyroids are sometimes separated from the thyroids, and in such forms as the elasmobranch fishes, the two parts of the suprarenal are represented by distinct organs, the interrenal and the adrenal bodies. In some cases the associated structures have a similar embryonic origin, but in the case of the pituitary and suprarenals the two parts arise independently.

Whether or not any functional significance is to be ascribed to the association of these different structures has not been determined. In case of the suprarenal glands a theory has been offered that the cortex, although it does not afford a potent extract, does elaborate a precursor of epinephrin, which is then transferred to the medulla to be transformed into the finished product. A similar theory has been held in regard to the pituitary. In neither case has conclusive evidence been offered as to the validity of the theory. Moreover, in the case of both the pituitary and the suprarenal bodies, the evidence of distinct functions of the component parts is fairly conclusive. So far as the writer is aware phylogenetic studies fail to throw any light on the problem, aside from showing that secondary displacements of tissues not infrequently occur as a result merely of major adaptive morphologic changes. The occurrence of hematopoietic tissues in the cavity of long bones shows that propinquity does not necessarily imply functional relationship.

The Endocrin Organs and Old Age

Whether endocrin factors play a significant part in the onset of the changes characteristic of senility has been debated but without any very convincing evidence having been adduced. Senescence is marked by a series of anatomical changes of a regressive or degenerative nature, such as might theoretically result from a precedent failure of the "regulators of metabolism," or, more specifically, of the stimulating and sustaining hormones.

Such changes occur in every organ and tissue of the body. The tissues either assume atrophic forms or are replaced by those of other character which are functionally less efficient. In the nervous system both the central and peripheral structures are affected. The nerve cells, as well as the medullary fibers, show atrophic changes with increased density and loss of lipoids. The muscles waste away, and the heart tends to become more or less fibrotic, but may show hypertrophy compensatory to changes in other parts of the circulatory system. The bones lose a portion of their organic matter, becoming brittle and to some extent showing osteoporosis. Ligaments and tendons lose their elasticity and show general wasting. The synovial structures likewise deteriorate. The skin changes characteristic of old age are known to all. Pigmentation, atrophy of sebaceous and sudoriparous glands and general wasting of both cutaneous and subcutaneous tissues occur. The hair generally becomes dry and thin but may show excessive growth in certain situations, in the eyebrows, at the external auditory meatus, or the anterior nares. In women more or less hair growth on the upper lip and chin is not uncommon. In the viscera general atrophic and fibrotic changes are common. The spleen, for instance, may be reduced to one-half its normal size. The prostate, however, tends to enlarge through overgrowth of connective tissue. The liability of the blood vessels to become hardened and infiltrated with lime salts is well known.

Extensive as are these anatomical alterations, the physical debility of old age is, according to Thewliss, even greater and in many instances not explicable upon a purely anatomical basis.

Goodpasture, in 1918, made an extensive report upon the changes incident to senescence. His work was based upon a study of fifty dogs. He has evolved a conception that "with a continued increase in structural intricacy, incident to aging, the body cells gradually lose their metabolic equilibrium, so that the ultimate conclusion of progressive cell differentiation is death. But it is possible for many cells to return to a more simple form in which special function is absent or subordinate to growth and division." This process of elimination of structural differences is called "de-differentiation." A de-differentiated cell may differ-

entiate again, re-forming structural substances similar to those formerly possessed, and perhaps function normally. But when de-differentiation has proceeded far enough, under abnormal conditions, a metaplastic transformation may result, the cells developing characteristics which they did not formerly have.

Some at least of the senile alterations suggest the operation of endocrin factors. The scantiness and dryness of the hair, the dryness of the skin, the manifestations of depressed metabolism in the osseous structures, and the tendency to chilliness are such changes as might result from deficient thyroid secretion. Indeed, it has been claimed that these alterations can to a considerable extent be obviated or ameliorated by the circumspect administration of thyroid gland substance. As a matter of fact, the thyroid gland in old age shows anatomical alterations such as atrophy and sclerosis, which might well result in functional deficiencies, but whether these changes antedate the senile manifestations just mentioned apparently has not been determined. In old dogs Goodpasture found the thyroid glands smaller than normal. He noted also a marked irregularity in the distribution of the colloid and occasional areas of metaplasia. In three instances multiple cysts were found; these were lined with three or four layers of epithelium and the layer nearest the lumen was partially or completely differentiated.

Little is known regarding changes in the parathyroid glands in old age. The tremors of paralysis agitans, which is not an infrequent disease of old age, have been ascribed to parathyroid deficiency and there are in the literature reports of successful treatment of the condition by parathyroid opotherapy. The evidence at present available does not permit any very definite conclusions, however, as to the importance of the parathyroid factor. Goodpasture noted little deviation from the normal in case of senile dogs.

The pigmentary alterations of the skin are somewhat suggestive of those known to result from adrenal deficiency. In view of the fact, however, that pigmentation of the skin can result from a variety of causes, such evidence is by no means convincing. In his senile dogs Goodpasture, as a matter of fact, found that the suprarenals were usually larger than normal and their surface was irregular with smooth and more or less spherical protuberances 1 to 20 mm. in diameter, usually multiple and occurring in both glands. There was commonly great irregularity in the architecture of the cortex due to a combination of atrophy in some parts and hyperplasia in others. There were no outspoken degenerative changes constantly demonstrable in the cells, but there were indications of a gradual disappearance and replacement of the parenchyma. Indirect evidence of degeneration was found in the presence in the lymph spaces of a considerable number of phagocytes filled with brownish, finely granular pigment. Hyperplastic changes were found in

all three zones of the cortex. In the medulla no disintegrative or degenerative changes were made out.

In case of one organ, the ovary, the evidence of an important relationship to bodily alterations in the latter period of life is adequate. The genital atrophy that follows the menopause in women is strikingly similar to that following removal of the ovaries at an earlier period. Such changes are atrophy of the uterus and Fallopian tubes, of the structures about the vulvar orifice, and of the breasts. As is well known, the ovaries after the menopause become shrunken and fibrotic, and their endocrin function supposedly becomes correspondingly depressed. The persistence of libido after the climacteric, however, is not so very uncommon, and this may indicate some persistence of endocrin activity in the ovary.

In case of the male, conditions are somewhat more complex. There is great variability in the sex manifestations of elderly men. Usually, perhaps, after middle age there is a gradual decline in libido and potentia which goes pari passu with the slowing down of general bodily activity. Cases are by no means rare, however, in which the sex life remains active even past the allotted three-score years and ten. In some instances indeed, there seems to be even an augmentation of the sex activities in the fifth or sixth decade. To what extent general bodily vigor is dependent upon gonadal functioning is not at all clear. In this connection Brown-Séquard's famous experiments upon himself suggest themselves. This able observer believed that as a result of subcutaneous injections of testicular extracts his vitality was greatly increased. Of recent years there has been a recrudescence of Brown-Séquard's ideas, based upon the claims of Lydston, Voronoff, and others, that old men can be rejuvenated by grafting into their bodies testicular material. Steinach has claimed (but others have denied) that a similar rejuvenation can be brought about merely by ligation of the vasa deferentia, an operation which supposedly results in augmented activity of the interstitial cells of Leydig at the expense of the atrophic seminiferous cells. That the Leydig cells may persist, or even be increased somewhat in old age, has been reported by several observers. The writer is not acquainted with any definite evidence, however, of a correlation between such persistence and the sex activities.

As to changes in the other endocrin organs in old age, little evidence is available. In his dogs Goodpasture noted the occasional occurrence of cysts in the hypophysis, but such have been reported also in younger animals. That the pineal organ and the thymus undergo at least some degree of atrophy, beginning at about the age of puberty, has often been claimed, but later investigators have maintained that age involution in these structures is less striking than was formerly believed. That the pancreas deteriorates in old age is probable from the fact that senile diabetes is not uncommon. According to Allen, there is a margin of safety

of some 700 per cent in the pancreas, hence such diabetes would indicate a high degree of functional insufficiency.

On the whole the evidence now available does not permit any very definite conclusions as to what extent endocrin factors play a causal rôle in senescence. That there is no inherent necessity of senile degeneration has been claimed by various well informed biologists. The forestalling of the degenerative changes would seem to depend upon the maintenance of anabolic activity in the body cells. The endocrin organs admittedly have an important influence on the fundamental metabolic processes. It would seem, therefore, that further study could profitably be devoted to a determination of the extent to which endocrin changes normally precede those in the body at large, and to what degree such changes may be prevented or even reversed by judicious endocrin therapy.

Endocrin Factors Determining Racial and Individual Characteristics

The fact that certain of the racial characteristics by which anthropological types are set off are not dissimilar to those resulting from certain ductless gland anomalies has not escaped the attention of speculative endocrinologists. Keith, for instance, has written engagingly upon this subject. In this connection we may consider especially variations in stature, in bodily and facial configuration, in pigmentation, and in growth and distribution of hair.

That the races of mankind vary markedly in stature is well known. The tall northern European is in striking contrast with the pigmy races, such as are found in Africa and other tropical or subtropical regions. The precise geographical distribution of such variants is a matter outside the scope of this work. Experimental and clinical investigations have shown that the hypophysis is capable of exercising a profound influence upon the length of the body and the limbs of the individual subject. This is well brought out in succeeding chapters on gigantism and dwarfism. At this point suffice it to say that it has been possible to show that many cases of gigantism have been characterized by enlargement of the hypophysis, as shown by skiagrams or measurements of the sella turcica, as well as by direct post-mortem examination. That hyperfunctioning of the hypophysis beginning before puberty leads to prolonged growth of the long bones and the trunk is generally accepted. On the other hand, hypophysial deficiency is ordinarily regarded as an important factor in dwarfism. A relative preponderance of hypophysial function, then, if it occurred as a racial characteristic, might well result in augmented average height, just as depressed functioning might lead to pigmy types.

Another possible factor in the regulation of height is the action of the

endocrin components of the gonads. Castration tends to result in delayed closure of the epiphyses and persistence of body growth past the normal age of puberty. This fact has long been made use of in case of farm animals. As is well known, the castrated cockerel develops into the overgrown capon. Various data on this point will be found in the chapter on "eunuchism." That the fervent, early maturing, relatively short races may derive their somatic and mental characteristics in part from relative preponderance of the gonadal hormones is possible if not probable, just as the more phlegmatic, tall, late maturing races may derive some of their characteristics from relative depression of these hormones.

Similarly the thyroid might be regarded as a factor in the determination of stature. The stunted cretin, whether human or experimental, is well known. There is in the literature no little evidence of an intimate relationship between the thyroid, the hypophysis, and the gonads. A theory that these three organs functioning synergistically and supplementing each other largely determine the height of the individual or the race would be quite tenable. For further data the chapter on "Hormone Factors in Growth and Development" may be consulted.

In addition to changes in general growth processes the endocrin organs are capable of conditioning various modifications of configuration. The heavy features, the protruding lower jaw with widely spaced teeth, the beetling brows, and the gorilla-like proportions of the acromegalic are well known. That there is a tendency toward modification in this direction during pregnancy has often been noted, and this tendency may be correlated with hyperactivity in the hypophysis, a condition first described by Erdheim and Stumme. Similarly, the configuration of the cretin is characteristic. The arrest of growth in cretinism affects the skeleton in general, but cranial changes are particularly prominent. The base of the skull, especially, fails to develop, with the result that the root of the nose appears to be flattened and retracted between the eyes; whereas the upper forehead appears to project. These are the features that, as Keith points out, give the Mongolian face its characteristic aspect. They are also to be traced in lesser degree in the Negro race. Indeed, in one aberrant branch of this race, the bushmen of South Africa, the thyroid-facies is even more marked than in the Mongolian.

The differences in skin and hair of various races are striking. Pigmentation is one of the characteristic results of suprarenal deficiency in man, and Keith is inclined to ascribe to such deficiency a significant rôle in the production of skin coloration in the darker races. The fact that suprarenal hypertrophy leads at times to marked hirsutism, whereas the darker races tend towards sparseness of hair, would bear out this assumption. On the other hand, suprarenal deficiency leads to bodily weakness, a condition that is not especially characteristic of the darker races. Also, suprarenal hypertrophy results in precocious puberty, whereas there is

no striking delay of puberty among the Negroes. In fact, the darker races tend to mature earlier than the light.

The theory that the human types are determined by endocrin factors has been pushed by certain writers of late years much further than indicated in the preceding paragraphs. Pende, for example, lays great stress on "endocrinopathic constitutions" as determining not only structural characteristics but also liability to endocrin and other diseases. That there is a fairly well marked "status thymolymphaticus" cannot be questioned. That the various endocrin glands may, by their inherent or acquired tendencies to over- or under-activity, materially modify the "constitution" is not intrinsically improbable. There is not, however, in the opinion of the writer, sufficient clean-cut evidence available upon the point to permit any very valuable generalizations.

While it seems a priori likely that variations in endocrin predominance or deficiency may lead to marked alterations in body structure of sufficient magnitude to serve as racial criteria, there is no theoretical necessity for assuming such factors, or indeed not any great philosophical gratification in so doing. In many instances we are perforce reduced to vague conceptions of precedent variations in germ plasm to explain somatic differences. That the sealion develops flappers, for instance, whereas the fowl develops wings and the dog legs, can scarcely be ascribed to the action of hormone factors, at least in the ordinary sense of the term. Similarly, the determinants of racial stature may also reside in the germ plasm, and this come to light in postpuberal development as a manifestation of inherent growth tendencies. Whether hormone determinants actually are involved in development of racial characteristics remains for future research to disclose. A first step towards a solution of the problem would be to make a careful study in the various races of the endocrin organs from infancy to early postpuberal life, determining both their relative weights and relative degree of secretory activity, and particularly determining whether endocrin activity precedes or accompanies the appearance of the characteristics ascribed to it. So far as the writer is aware, no significant data along this line have been secured.

Methods of Investigation of Endocrin Functions

Two general types of investigation have been widely utilized in the study of the functions of the endocrin organs, namely, augmenting and decreasing by various methods the function in question. In frequent instances a sequence of the two methods, one being used as a check on the others, has yielded important data.

Several different methods of increasing the hormone content of the blood have been employed, such as administration of extracts or organ

substance by mouth or in various other ways, grafting into the body viable endocrin tissue, or increasing the output from the individual glands by massage or stimulation of their secretory nerves. A considerable amount of valuable information has also been obtained from the study of human beings or animals in which spontaneous overactivity of the various glands occurs.

Functional deficiencies can be created by gland extirpations, by injecting substances to cause bland infarcts in the glands or by ligating the blood vessels supplying the organs in question. Clinical observations of patients with spontaneous or surgical gland deficiencies are also of great value. Some of our most valuable data have been obtained from such observations.

Augmentation of Hormones.—*Intravenous Injections.*—Oliver and Schäfer's early experiments on the effects of suprarenal extracts administered intravenously made a profound impression and led the way to a great number of other experiments of a similar sort with many gland substances. The method is relatively easy and direct and, upon superficial consideration, well calculated to afford important data in endocrin physiology. Many investigators have utilized the method, however, with scant appreciation of the numerous pitfalls with which it is beset, and have drawn sweeping conclusions that the data secured by no means justified.

The numerous possible sources of error in such experiments were early recognized and pointed out. Gley in 1899 wrote: "It is necessary to ask oneself if all the glands in question normally produce substances identical with those the actions of which are manifested by their extracts. In fact, the substances contained in the extracts may not exist in the living glandular tissue; furthermore nothing proves a priori that, if they are formed in the living gland, they regularly leave it by the blood vessels in order to exercise their influence on the different arterial regions of the organism. It is necessary that the demonstration given for the suprarenal bodies be also supplied for the other glands" (Gley, 1917).

In 1899 Lewandowsky also pointed out that we cannot draw any valid conclusion as to the action of any organ in the body from the effects of extracts of that organ injected into the blood.

Biedl has also warned of the fallacies inherent in sweeping deductions from this type of experimentation. "In order to prove conclusively that in a given organ extract a hormone is contained, which results from the endocrin activity of that particular organ, it is necessary first to establish two postulates, which, in the present state of our knowledge, offer great difficulties. First it is essential to secure a thorough knowledge of the chemistry of the active substance. In this attempt much remains yet to be done. A second and equally important postulate lies in the proof that any given active substance demonstrated in the organic extract is produced in the gland during life and is discharged into the circulation."

It should always be borne in mind that a gland extract is a heterogeneous mixture of many substances. Living tissue is made up of systems of highly labile components. Many of these undoubtedly are changed both physically and chemically during the progress of the death processes in the tissues. The disintegration and recombination of these various components may give rise to a great variety of end products which in the living gland were nonexistent or occurred to a much less extent than in the gland extract. Furthermore, even though a given product found in the gland extract exist as such in the living organs, it does not necessarily follow that this product as such is discharged into the circulation. It might be merely an intermediate product in process of further elaboration. It is obvious in the nature of the situation that in addition to any hormone that might occur in a given gland extract numerous nonspecific substances are certainly present. When given by mouth these substances may be digested or otherwise disposed of and play a negligible or relatively unimportant part, but when the extracts are introduced directly into the circulation, as commonly is the case, they often play a predominant rôle in the reactions.

One such nonspecific substance which is likely to be found in any tissue extract is cholin. This is a powerful vasodepressant. This substance has received much attention at the hands of investigators and observers are likely to be on their guard concerning it. More recent work shows, however, that it plays a less important rôle in injection experiments than was formerly supposed. Nucleoproteins also are always found, but these have come to be recognized as relatively unimportant in that they do not give rise to any immediate striking reactions. Histamin is another highly potent substance which can be demonstrated in gland extracts from a variety of sources. This may play an important part in the reactions to the extract. Indeed, so struck was Abel by this possibility that he for a time regarded histamin as the actual "active principle" in extracts of the posterior lobe of the hypophysis. Largely through the work of Vaughan and his collaborators, we have come to recognize that the most harmless protein substances may, during the process of their disintegration, give rise to highly toxic material. It is not unlikely that the split protein toxins have played a significant part in experiments on gland injections. The work of Jobling, Bronfenbrenner and others has brought out clearly the importance of the tryptic enzymes of the blood in the formation of such toxins. Unless one is on his guard in making gland extracts, these toxins can readily be formed, and can either give rise to reactions in the experimental animal or can mask the effects of any specific substance which may be present in the extract. Anaphylactic shock, which may be merely a special phase of protein intoxication, may enter in as a disturbing factor in case the experimental animal has been previously sensitized to any protein present in the gland extract. There is ground for

believing that even putrefactive products have in the past figured as specific hormones.

The fact that some at least of the hormones will withstand boiling without serious loss of potency affords a means of eliminating the disturbing factors that reside in the protein content of gland extracts. If boiled in weakly acid medium the solution is both sterilized and freed from protein. If the filtrate from such a boiled extract is hermetically sealed or evaporated to dryness it may retain its potency for long periods.

Investigators in the past have felt free to use such reagents as strong acid or alkali in preparation of extracts in which they hoped to demonstrate hormone constituents. In drawing conclusions from the use of such gland materials, particular caution is necessary. The body has at its disposal as a menstruum only the tissue fluids which differ relatively little from simple isotonic saline solutions. Accordingly, any "hormone" that requires for its "liberation" such substances as sulphuric acid or potassium hydrate is probably nonexistent in the normal gland. It is true that through the presence of specific enzymes the body is able to form, even in a simple menstruum, elaborate products; but there is no convincing evidence that such enzyme factors are involved in hormone production. More than one elaborate report in the literature if judged by the criterion just discussed would be without significance.

Many, if not all, unboiled tissue extracts contain substances that are likely to induce intravenous coagulation. Kephalin is particularly important in this regard (Howell). If massive clotting should occur death would at once ensue and the only possible erroneous conclusion that might be drawn would be that the substance was "toxic." Localized clots, however, may be carried to or formed in the nervous system or elsewhere and produce striking effects that upon superficial consideration might seem to be the result of specific hormones. The inconstancy of such results are sufficient to rule out specificity.

One striking fact noted in connection with experiments on the pharmacodynamics of gland extracts is that a given apparently specific reaction can be obtained from extracts of several different glands. For example, augmented flow of milk from the lactating mammary glands has been reported following the administration of extracts of the posterior lobe of the hypophysis, the corpus luteum, the uterus, the lactating mammary glands, the thymus, and the pineal. Likewise, contractions of the bladder have been reported following injections of extracts of the thymus, the thyroid, the testicles, the prostate, and the pancreas. Following the reasoning which has been employed in many reports of endocrin researches, each of the glands mentioned may be regarded as normally controlling the activity of the mammæ or the bladder. Such multiple control is, to say the least, highly improbable.

Another experimental difficulty encountered in experiments with

gland extracts is that a sort of immunity is developed. As long ago as 1898 Howell observed this in connection with studies on the vasomotor effects of pituitary extracts. He observed that although an augmentation of blood pressure resulted from the first injection, a second shortly thereafter might give rise even to a depression. This observation was confirmed a year later by Schäfer and Vincent. Étienne and Parisot (1908) have observed that repeated injections of pituitary extracts fail to provoke an increase in cardiac discharge such as is observed after the first injection. This observation was confirmed by Salvioli and Carraro. Similarly, although a first injection of pituitary extract may cause marked contraction of the bladder, this becomes less and less extensive with succeeding injections. Schäfer and Herring, in their classic observations on the diuretic effect of pituitary extracts, noted that a second injection is likely to cause much less vasodilatation in the kidney and correspondingly less diuresis. That repeated injections of epinephrin may produce successively decreasing effects is well known. Roger and Josué have observed that a first injection of extract of intestinal mucosa causes a marked fall of blood pressure, but that such a result is not obtained from a second injection. Gley and Champy have made a similar observation as regards extract of corpus luteum (Gley, 1917). That such effects are not due merely to the introduction of foreign proteins is shown by the fact, observed in the writer's laboratory, that marked fall in blood pressure may result from the injection of freshly prepared extracts of the experimental animal's own pancreas or salivary glands.

In the investigations of the physiology of the endocrin glands by injection experiments due regard should be paid to the quantitative aspects of the research. When, at a single dose, as much material is administered as a normal animal could be expected to secrete in several hours, no conclusions can be drawn as to the physiological aspects of the hormone in question. At best such a research can afford data of pharmacological value. As a case in point, the greatest amount of epinephrin that can be obtained from the suprarenal glands by stimulation of the splanchnic nerve is, according to Osgood, but one two-hundredth of the quantity necessary to provoke glycosuria. Yet the glycosuric effect of epinephrin has been made the basis of much theorizing as to the physiology of the suprarenal glands. A theory of carbohydrate metabolism, prominent a few years since, had no more secure foundation than the fact that it is possible, by the use of large doses, to produce epinephrin glycosuria. In classroom demonstrations from which students are supposed to make deductions regarding suprarenal physiology, it is the custom to inject from a half to one milligram of epinephrin at a single dose. Yet the researches of Stewart and Rogoff, Hoskins and McClure, and others, indicate that the output from these glands does not transcend two ten-thousandth of a milligram per kilogram per minute. Neither by direct massage of the

suprarenal glands nor by stimulation of their secretory nerve can more than a very moderate rise of blood pressure be evoked. In view of the fact that the qualitative reaction to epinephrin may be exactly reversed by changes in the quantity administered, this factor is of considerable theoretical importance.

Another difficulty is that abnormal products undoubtedly vary greatly from one extract to another, even of the same gland. Among the factors which may cause such variation are the time that elapsed between the preparation and use of the extract, the degree of autolysis or even putrefaction, the dilution, the degree of heat used in preliminary processes, and preservatives added. In the presence of so many variables and these often quite uncontrolled, how can any valid conclusions be drawn? It is obvious that the utmost caution must be observed. At most such experiments serve merely to demonstrate pharmacodynamic constituents in the extracts as finally prepared. This is merely a first step in the demonstration of the existence of a hormone. Positive results establish no more than a certain degree of antecedent probability that a hormone is present. It remains to be proved that the active substance is not an artefact or that it exists in the blood or lymph coming from the organ in question.

Despite the inherent defects in the method of intravenous injections and the frequently enunciated warnings against the numerous sources of error in the use of the method, the literature discloses a voluminous series of reports of researches based on such injections. Nor have the authors hesitated in many cases to offer sweeping deductions from observations so obtained. As recently as 1918 Marfori published an elaborate paper in a leading biological journal, announcing the discovery of a new hormone, "lymphogangline," elaborated by the lymphatic glands. The observations upon which the claim is founded are essentially that extracts of lymphatic glands reduce the frequency of the heart beats, lower the blood pressure, contract the pupil, and hinder the production of epinephrin glycosuria. This paper is reviewed at length by Vincent (1918). If one were to grant the validity of such claims, the number of hormones in the body is limited only by the patience and skill of the investigator in isolating tissue components. There is little doubt that similar "hormones" could be isolated from the vocal cords, from the vermiform appendix, from the iris, or any other body tissue.

While it is historically true that many significant data have been obtained by the method of intravenous injections of tissue extracts, yet it is obvious from the foregoing discussion that from such experiments alone only tentative conclusions can be drawn and that the investigator must be rigidly on his guard against pitfalls at every step.

But in spite of the inherent sources of error in the use of gland extracts by vein, many instructive results may be obtained from this type of experimentation. It has certain outstanding advantages. Any hormone

present is at once distributed throughout the body and the maximal effects are seen before it is destroyed or excreted. A large proportion of our significant data as regards suprarenal physiology have been derived from the study of the results of intravenous injection.

Administration by Mouth.—The administration of gland extracts by mouth has been of great use clinically, as in the thyroid treatment of myxedema and cretinism. Various other examples of the effectiveness of oral administration are discussed in the chapter on Opotherapy. In experimental work the method has been most useful in the study of the hormone factors in growth. Guddernatsch's well-known experiments on the influence of thyroid substance on the metamorphosis of tadpoles is a case in point. Numerous other examples will be found in the chapters on the physiology of the various endocrin glands. In such work the possible importance of nonspecific substances in the material fed should always be kept in mind. The presence of nucleoproteins may be an important factor in results. If the experimental animal were not receiving otherwise an adequate supply of protein, the administration as gland substance of relatively small quantities of this important food element might cause considerable change in growth. The researches of Funk, Mendel, McCollum and others show that mere traces of certain as yet unknown substances may exercise a profound influence upon the growth and developmental processes. These substances, the vitamins, as Funk calls them, must always be excluded as the determining factor in results. In all feeding experiments the control animals should be supplied with some indifferent tissue substance equivalent to the gland material administered to the experimental animals, or else both experimental and control animals should receive a maintenance ration so complete that the addition of the gland substance can play no significant rôle merely as food or as a conveyor of vitamins. Another source of error is growth experiments resides, according to Robertson (1917), not in the substance fed but in a failure to recognize certain essential features in the process of growth itself. "There is," according to this investigator, "a widespread and mistaken tendency to regard growth as a single process and to infer that, if a given substance or condition accelerates the growth of one particular tissue at any given time, the same substance or condition will also accelerate the growth of other tissues or of the same tissue at a different physiological age. Growth, on the contrary, is a multiplex phenomenon and factors which favor the growth of one particular type of tissue or the growth of the whole animal at one particular age may actually exert the reverse action upon another tissue or at another stage in the growth of the animal concerned."

The necessity of controlling rigidly the environmental factors would seem so obvious as to require no mention. Notwithstanding, there can be found in the literature more than one elaborate report of researches in

which this factor was ignored or inadequately controlled. The number of animals in a cage, inequality in the size of animals in a given group, variations in lighting, exposure to drafts, differences in the distance from the source of artificial heat, differences in cleanliness of cages, different degrees of infestation with parasites—these are some of the variables which can easily creep into growth experiments. Sex differences, which may be marked, should always be taken into account. The desirability of selecting experimental and control animals from the same litters is obvious, but sometimes is overlooked.

In the last analysis experiments of the type discussed amount to statistical studies. Accordingly, all the criteria of statistical science should be observed in such researches. The observance of such criteria has, as a matter of fact, been the exception rather than the rule, and many of the reported results are of correspondingly slight value. A high degree of "spontaneous variability" is characteristic of the laboratory animals that are most commonly employed. To demonstrate, therefore, that the administration of a given gland substance brings about any characteristic change in growth or organ weight, a large number of cases is usually essential. In the face of such high variability and of the possibility of mere coincidence, the attempt to draw valid conclusions from observations on, say 10 animals, betrays an ignorance of the elementary principles of statistical science. "Averages," under such circumstances, are meaningless, though frequently cited as the gist of results secured.

As a variant upon oral administration, sublingual is sometimes employed. It is said that the oxytocic effect of pituitrin can be obtained in this way. The method has been little used either clinically or in experimentation.

Administration by Rectum.—The effects of the digestive enzymes upon the endocrin gland substances are largely unknown. In case of the thyroid the fact that ingestion of gland substance is capable of warding off the ill effects of deficient secretion shows that we are dealing with a stable body. In the case of epinephrin, on the other hand, oral administration is quite without effect, as judged by pharmacologic criteria. It is true that many claims have been made of the efficacy of such administration clinically, but therapeutic evidence of this sort is proverbially fallacious. It has been stated that in the case of most of the endocrin glands better results are secured by rectal than by oral administration. This possibility should be thoroughly investigated, both on account of its clinical bearing and its importance in experimental work. The writer has recently observed that in case of epinephrin rectal administration has approximately the same degree of efficacy as has hypodermatic. In some experimental animals no effect could be detected from doses as large as 5 milligrams, even when so sensitive a test object as the denervated gut was used. In other cases slight changes in blood pressure and marked in-

hibition of peristalsis in the intestine resulted from the administration of as little as 1 milligram.

Parenteral Injections.—In some instances, when fairly rapid but not instantaneous results are desired, the gland extracts can be introduced into the intramuscular or the subcutaneous tissue spaces. Absorption then takes place into both the lymphatic and blood capillaries. The same is true of extracts introduced into the peritoneal cavity. In this case the absorptive function of the omentum is probably of considerable importance. Parenteral injections have certain advantages: the extracts are spared the possibly deleterious action of the digestive enzymes of the alimentary tract. There is less danger to the experimental animal as from thrombosis, and less disturbance of body functions than when intravenous injections are employed. The possibility of infection and consequent abscess formation is an obvious disadvantage which must be guarded against. In case of epinephrin, at any rate, there is also the possibility of tissue necrosis due, supposedly, to prolonged local ischemia. In case of intramuscular injections the promptness of the appearance of the reaction is little less than when the extracts are given by vein, but the relatively slower absorption is likely to result in quantitatively less marked, though more prolonged reactions. When dilute epinephrin is administered intramuscularly, the fact that it dilates the surrounding blood vessels probably accounts to a considerable extent for the rapidity of its absorption. On a priori considerations it might be desirable to incorporate the gland material under investigation in relatively insoluble menstrua in order to bring about a slow but prolonged absorption of the material, thus simulating its normal discharge from the glands. In a series of unpublished experiments, the writer attempted some years ago to produce in this way the equivalent of hyperepinephrinemia, but local tissue necrosis prevented any conclusive results.

Intrapulmonary Injections.—That the intrapulmonary route is not without advantages for the administration of epinephrin was reported by Auer and Gates. The capillary circulation in the lungs is relatively profuse and the drug is separated from the blood stream by only the thin alveolar and capillary membranes. Absorption is correspondingly prompt. The method would seem to be particularly well adapted to getting epinephrin quickly to a failing heart. At the same time one danger in the use of that substance in such cases would probably be obviated, namely, the danger of inducing fibrillation of the ventricle, such as may result when the injection is made directly into the heart. When epinephrin is thus introduced it is likely to be carried in too great concentration to the coronary vessels or be deposited in the ventricular wall itself, thus causing an overstimulation and the result mentioned. The suitability of intrapulmonary injections as a method of administering other hormones than epinephrin remains yet to be determined. Except

possibly for pituitary hormone, it would not seem to be a promising method. The difficulties and dangers of the method are more or less obvious.

Direct Application to Tissues.—In many cases instructive results are obtainable by application of endocrin extracts directly to the living tissues. The clinical application of epinephrin to blanch the nasal mucosa or the conjunctiva is a well-known procedure that illustrates this method. The epinephrin spray for the relief of asthma is another example. Hartman has used a somewhat similar procedure in a study of the vasodilator mechanisms. He applied epinephrin directly to various sympathetic ganglia and noted the effects in the peripheral tissues. In the use of the direct application method for experimental purposes the tissues are ordinarily removed from the body and the extracts either applied to the surface or introduced through an isolated artery. One of the best methods of determining the epinephrin content of a given fluid is to pass it through the capillary circulation of the frog's hind legs. This is the so-called Trendelenburg method. Mammalian tissues employed for this type of experiment are kept in warm oxygenated Tyrode's solution or similar fluid. In favorable cases they will survive for hours. Ott and Scott published many investigations based upon this technique. The rabbit intestine method for assaying epinephrin is a well-known example. In such experiments, also, the quantitative factor should receive due regard. A short segment of gut, for example, is but a small portion of the total body tissue and would, if left in the body, be exposed to a correspondingly small fraction of any given amount of circulating hormone. In individual experiments the dosage should be correspondingly restricted. Just how much allowance, however, should be made for decreased irritability of the test tissues when removed from the body is unknown.

Organ Grafting.—In some instances organ grafting has been used to augment the quantity of circulating hormones. In the early development of the thyroid treatment of myxedema this procedure was successfully employed. The literature contains many reports of attempts to alleviate clinical symptoms by this method. An example which has recently evoked much interest, especially upon the part of the laity, is the engrafting of testes with the idea of rejuvenating elderly men. There are numerous technical difficulties, however, which limit the use of the method in practical experimentation and as a clinical procedure. The only way in which grafting can be accomplished with anything like constant success is by the employment of the individual's own tissues (autografting), and that procedure is of obviously restricted utility. The more closely related are the host and the donor of the tissue, the more likely is the graft to "take." Transference from one species to another (heterografting) is almost never successful. At best the tissue is soon absorbed and the net result is equivalent to that of a parenteral injection.

Loeb has made an intensive study of the reactions of the host to the implanted graft. The destruction of the graft is due to two processes: a development of connective tissue throughout the tissue and consequent "strangulation" of it and an invasion of lymphocytes. Leucocytic invasion plays a minor rôle. A close study of the engrafted tissue showed that the lymphocytes acted as primary destructive agents and not merely as scavengers. The line of demarcation between the invaded and the destroyed areas was sharp; there was no transitional zone of degenerating tissue such as would have been found if the lymphocytic invasion were secondary. Loeb ascribes both the lymphocytic infiltration and the connective-tissue cell proliferation, which occurs in the graft, as due primarily to the changes in the metabolism of the invading cells rather than to any hostile reaction of the host. The altered metabolism gives rise to toxins which attract lymphocytes and change the activity of the connective-tissue cells. The more closely related are the host and donor the less active is the formation of these toxins. As a secondary reaction the proteins of the invading cells may act as antigens and stimulate the production of antibodies upon the part of the host. These antibodies may then serve to accelerate the metabolic changes in the invading cells and thus contribute to the final destruction of the graft. In view of the important part played by lymphocytic infiltration and the well-known destructive effect of X-rays or radium upon lymphocytes, it is possible that the irradiation of the graft might add to the percentage of successful "takes."

According to Halsted, grafts ordinarily do not survive unless there is a preëxistent physiologic deficiency of the gland in question.

To secure nutrition adequate to keep the graft alive until it can become vascularized is difficult. To accomplish this the tissue is often cut into thin slices and inserted into some highly vascular organ such as the spleen. The sex glands seem to lend themselves especially well to this type of experimentation. Wheelon and Shipley have submitted graphic evidence of the functional integrity of testicular transplants. They found that castration in dogs resulted in a material decrease in sympathetic irritability as manifested by the vasomotor response to intravenous injections of nicotine, which is a selective sympathetic stimulant. Later, a considerable period after testicular tissue was implanted in the experimental animals, the reaction to nicotine was materially augmented.

In physiological experimentation some method of creating a clean-cut excess of hormone production is greatly to be desired, as producing the equivalent of a functional overactivity of the various endocrin organs. Multiple grafting as a means to this end has as yet not been successful. Possibly in the future some method of augmenting the tolerance of the host for transplanted tissue may be evolved and lead to valuable results. Up to the present time organ grafting, as an experimental method, has been of value chiefly as a check upon extirpation experiments. The

voluminous literature on organ grafting has recently been reviewed somewhat extensively by Mauclaire (1920).

Nerve Stimulation.—In some respects stimulation of the secretory fibers to a given gland is the most satisfactory method of augmenting its hormone output. The secretion thereby secured is supposedly normal in quality and not greatly outside physiological units in quantity. For this among other reasons a definite knowledge of the secretory innervation of all the endocrin organs is needed. In case of the suprarenals and the thyroid glands only is anything like satisfactory information available.

Artificial stimulation of secretory nerves ordinarily involves a considerable degree of trauma, as well as the use of an anesthetic, both of which detract from the adequacy of the method to reproduce physiological conditions. To meet this difficulty Cannon has attempted to employ the method of nerve grafting, using the phrenic as a constantly active source of impulses. The method is technically difficult and was abandoned by Langley years ago as not feasible. Cannon succeeded in a few cases, however, in obtaining results strongly suggestive, at least, of functional overactivity in the thyroid gland when the central end of the phrenic nerve was sutured to the peripheral end of the cervical sympathetic. The resulting manifestations included, particularly, markedly augmented basal metabolism. Troell and Marine attempted to repeat the work, but without success. The method is theoretically an ideal one to produce pure physiological augmentation of gland functions under controlled conditions. The most striking advantage is that there would be no question as to what is the primary cause of any effects produced, a question which always arises in a baffling way when spontaneous overactivity of different endocrin glands is studied. It is greatly to be hoped that the technical difficulties may be overcome and the method fulfill the promise it offers of unraveling some of the most puzzling problems in this field of research.

Maternal Administration.—Several years ago the writer experimented with a method of creating an excess of hormones in the circulation of developing fetuses by administering to the mother a corresponding gland substance, either by feeding or by injections. The method offers two theoretical advantages: the experimental animal is treated at the most plastic stage of its existence when maximal effects would be produced, and the brunt of the experimental procedure is taken by the mother, which supposedly would be less likely than the young organism to suffer from incidental derangements due to the gland administration. The offspring of females to which suprarenal substance was administered were found to have smaller suprarenal glands than normal newborn animals of the same species. This suprarenal hypoplasia was interpreted as a reaction to an excess of circulating suprarenal hormones. The interpretation obviously assumed that glandular hyperplasia or hypoplasia may be due to the operation of the chemical law of mass action, whereby a physiological

optimum of circulating hormones is maintained. The chief apparent defect of the method is the difficulty of interpreting any results secured. There are present all the possibilities of interaction among the endocrin organs of both mother and fetus. The actual practical utility of the method has not been adequately determined.

Clinical Studies of Excessive Hormone Secretion.—Some of the most significant data in regard to the internal secretions have been obtained by the study of patients suffering from "spontaneous" overactivity of endocrin structures. The functions of the pituitary gland, for instance, were completely unknown up to the time Marie noted a relation between changes in that organ and the development of the symptomatology of acromegaly. The most striking information which we have, pointing toward the function of the suprarenal cortex, is that subjects having neoplastic hyperplasia of that tissue are likely to show anomalies of the sex functions. These are, in the female, "masculinization" and in the male exaggerated development of the secondary sex characteristics. The pertinent data are discussed in a subsequent chapter. Many of our ideas as to thyroid physiology have been derived from a study of the symptomatology of the thyrotoxicoses, particularly those due to toxic adenomata. Similarly, clinical studies have added largely to our knowledge of the physiology of the ovaries and of the internal secretion of the pancreas.

This type of investigation, however, is beset with many difficulties. The chief of these, perhaps, is to determine what is the primary and what are secondary factors in the pathogeny of any given clinical syndromy. That the various endocrin organs are intimately interrelated and materially influence the functions of each other is generally believed. When associated with a given syndromy some endocrin gland is found to show hyperplasia the most obvious conclusion would be that this is a sign of overactivity in the gland and that the overactivity is the essential etiologic factor. Such an assumption is, in fact, usually made. In most cases, however, the organ hyperplasia may as well be regarded as a secondary effect of the same noxa as that which produced the syndromy. In other words, the hyperplasia may play a concomitant rather than a causal rôle. This point is illustrated by the unfinished debate now going back for years as to whether the thyroid hyperplasia in Graves' disease is a primary or a secondary manifestation of the disorder. The obviously necessary check on this type of study is to produce the symptoms of the patient by augmenting in a normal subject his supply of the hormone in question. As regards the thyroid this experiment has been made both in human and in animal subjects. In no case has the symptomatology of Graves' disease been thus reproduced in a manner entirely satisfactory, despite frequent claims to the contrary. In Carlson's laboratory desiccated thyroid was administered in large amounts but without the production of anything at all closely similar to the clinical picture of exophthalmic goiter in

either man or animal. Nothing approaching experimental acromegaly from pituitary administration has ever been reported.

Depression of Hormones.—Several methods of creating endocrin gland deficiencies have been employed. Some of these are surgical extirpation, producing bland infarcts in the glands, ligating all or part of the blood vessels leading to or from the structures, injecting boiling water or injurious chemicals into the organs in question, or the injection of specific cytolytic sera with a view to causing selective destruction of particular endocrin cells.

Gland Extirpations.—The most common method of creating a functional deficiency is the obvious one of removing all or a portion of the gland in question. With the development of modern surgical technique this method has come to have the utmost importance. The earlier investigators, however, had little confidence in results derived from this type of experiments. Schiff's early observations, for instance, on the effects of thyroid extirpation were received with little favor, being commonly ascribed merely to suppuration or to the injury of important nerves. The method is particularly adapted to investigations of the problem as to which endocrin glands are essential to life. But even in such investigations, concordant results have not in all instances as yet been reached. For example, Cushing maintains that complete removal of the pituitary gland is inevitably fatal, while Aschner, another skilled scientist, is equally sure that animals may survive the operation. One maintains that death following extirpation of the gland is due to incidental trauma or hemorrhage—the other that survival when it occurs is to be ascribed to bits of gland left behind in the operation. That small residual fragments may survive and hypertrophy is well known. An important complicating factor in many cases is the existence of small masses of aberrant tissue lying at some distance from the main gland. Accessory thyroids may be found anywhere along the trachea. Outlying suprarenal tissue is not uncommon, along the course of the aorta and even as far away from the gland proper as the epididymus. Parathyroids may occur in various parts of the neck as well as in the thymus. In case of the guinea-pig, at any rate, Park has found that detached bits of thymus tissue are so common as to render total extirpation of the gland, such as has frequently been reported in this animal, quite out of the question. The possible existence of these aberrant structures in any given animal introduces an unavoidable element of uncertainty. Nor will a careful autopsy in all cases determine whether the object of the experiment has been attained. Unless complete serial secretions of all possible tissues that might contain accessory glands are studied, such may easily escape detection. In many instances such complete study is obviously impracticable.

In gland extirpations the actual or the electrocautery has in some instances distinct advantages over scalpel or scissors. It is especially well

adapted to the destruction of small organs, such as the parathyroids. The writer found it an excellent method of destroying the suprarenals and other endocrin glands in such small animals as newly-born guinea-pigs. It is both more expeditious and less likely to result in hemorrhage than are cutting operation.

Infarction.—Bland infarcts can be produced by injecting fine suspensions of inert insoluble material intc the arteries leading to the different glands. Tobacco seed or lycopodium spores are most commonly employed. This process involves comparatively little trauma and can be regulated to some extent to produce various grades of deficiency. It is a method, however, somewhat difficult to control with any satisfactory degree of accuracy, and so far has not led to any very striking results.

Ligation of Blood Vessels.—Ligating the blood vessels of a given organ in order to decrease its function is employed in both clinical and experimental practice. It is a well-known method of treating exophthalmic goiter in patients who are in too precarious a condition to undergo thyroidectomy. For experimental work the method is in most cases unreliable. In cases in which it is desired completely to occlude the circulation small vessels may be left untied and these quickly enlarge; or capillaries from the surrounding tissue may soon grow into the ischemic area and vascularize it, thus permitting the peripheral parts of the gland to hypertrophy and continue to function. In case of the suprarenal glands, the loss of which is rapidly fatal, ligation of the blood vessels seems to be essentially equivalent to extirpation. When complete occlusion of the circulation of a given gland is desired this may often be expeditiously accomplished by passing beneath the gland in situ a suitable needle carrying two ligatures. If one of these is utilized to form by constriction a pedicle beneath the gland on each side, and is then drawn tight, complete isolation is necessarily secured.

Interstitial Injury.—Of the various methods of destroying the tissues by the use of injurious materials, the injection of hot water is probably the best. The method is relatively safe, no harm being done if the fluid penetrates a blood vessel, whereas in case of chloroform, chromic acid or other escharotics they are likely to escape into the circulation and produce serious or even fatal injury. The method has been relatively little used in experimental investigations, although it is well known as a method of treating exophthalmic goiter. Of recent years injections of boiling water or of quinin and urea hydrochlorid have been most frequently employed. An obvious disadvantage of the injection method is the difficulty of control.

Specific Cytolysis.—After the discovery of the possibility of inducing an increase in the cytolytic power of the blood by the injection of specific antigenic cells, a hope was entertained that the method would prove valuable in endocrin research. It has been reported that if an animal

be given a series of injections of spermatozoa its serum acquires the power of destroying such cells without greatly affecting other kinds. Efforts have been made to induce a similar cytolytic power for hormone-producing cells as, for instance, those of the thyroid gland. Such a serum might then be injected into an experimental animal or a patient and cause disintegration of the thyroid tissue in situ. The method has not as yet proved entirely satisfactory. The cytolytic sera produced have not been sufficiently specific in action, and have destroyed other tissues in addition to those at which the experiment was aimed. The method is being further developed, especially by the Japanese investigators, at the present time. If the experimental difficulties could be surmounted the method would adapt itself almost ideally to numerous investigations and as a substitute for surgery in clinical practice.

Clinical Studies.—Many of the most significant data regarding hormone deficiencies have been derived from careful study of patients suffering from endocrin gland defects. Addison's discovery that deficiency of the suprarenal glands results in muscular and circulatory weakness remains as probably the most significant information yet offered bearing upon the physiology of these glands. Scarcely less significant has been the discovery of the relation of the thyroid glands to myxedema and cretinism. The relation of the gonads to the development of secondary sex characteristics has been familiar knowledge from earliest times through observations of eunuchs.

In cases of frank primary deficiency of some one endocrin organ the problem is relatively simple. But as it presents itself clinically the problem is very frequently complicated by the possibility of interrelations among the various glands. A given cause may act simultaneously on several members of a related congeries of organs producing a hypertrophy due to overfunction in each. But a hypertrophy of one of a related pair may also be due to the vicarious assumption of the function of the other. This is a common interpretation of the pituitary hypertrophy which follows thyroidectomy. When one organ normally exercises a check upon another, hypertrophy of the second may result from a depression of the activity of the first. If, on the other hand, one organ normally stimulates the other, as the thyroid does the suprarenal, hypertrophy in the second may be due to overactivity in the first. In view of these different possibilities of interpretation to determine in case of any observed clinical phenomenon its actual cause is frequently difficult or impossible.

Moreover, primary and secondary causes may be inextricably mingled. In the latter case various obscure pluriglandular syndromes may arise. The indefiniteness of the phenomena observable in such cases has led to much speculation and premature theorizing, which have, to a considerable extent, cast discredit upon the recorded data themselves. The plurigland-

ular syndromes should receive the most careful study in life and, if death supervene, painstaking post-mortem investigation. To elucidate this type of disease, however, the conventional autopsy is practically useless. Particular attention should, of course, be given to the various endocrin glands. The tissues should be fixed as soon as possible after death and later studied in section after appropriate staining, with particular attention to mitochondria and other evidences of secretory activity. The weight of the glands in relation to each other and to the body weight should be determined, as should the weights of the various gland components. Hammar (1920) has developed the methodology of this type of research and has emphasized the great need for extensive studies along these lines. Difficult as is this type of investigation, it offers promise of solving some of the most baffling problems now confronting the clinical endocrinologist.

Conclusion

From the data of the foregoing discussion it appears that research in the field of endocrin biology is beset with difficulties on all sides. In many investigations of the past the difficulties have been unappreciated or ignored. In a field in which a rigidly critical attitude is indispensable, careless credulity has been much in evidence. This is possibly an explanation of the fact that despite an immense amount of patient labor relatively few facts of fundamental importance are firmly established. None of the experimental methods applicable to this field of investigation is free from defects. The development of our knowledge has been correspondingly delayed. It is only by the use of all available procedures, checking one against another, that we may hope ultimately to acquire an understanding of the significance of hormone factors, either physiologic or pathologic, in the animal economy. Slow as this method necessarily is, nothing is likely to be gained by premature theorizing, however brilliant. In the past this has perhaps afforded some aid, but certainly has contributed much confusion. It is not likely to be more efficacious in the future. It may not be ungracious to conclude, in the words of Elliott, that in endocrinology as in other fields, "Medicine owes no thanks to him who, without proof, would formulate her theories."

History of Endocrin Doctrine ..... *Fielding H. Garrison*

Prehistory of the General Doctrine of Internal Secretions—Descriptions of Various Diseases Stressing the General Doctrine—Series of Experiments on the Physiology and Physiological Surgery of the Ductless Glands—Gradual Acceptance of the Doctrine.

History of Endocrine Doctrine*

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In the following paragraphs will be presented, in brief scope, the outstanding features in the development of the endocrine doctrine, as we know it to-day. While many of the data making up this chapter will be found treated at greater length in the sections devoted to each of the endocrine organs, it is thought that a bird's-eye view of the field as a whole may be helpful.

Since the development of the bacterial theory of infection, there is probably no pathological concept that has latterly so dominated modern medicine as the doctrine of the internal secretions of the ductless glands. In virtue of this theory—which, like that of the specific infectious diseases, is founded upon rigid laboratory experimentation—we are what we are, bodily, mentally, sexually, emotionally, facially, largely through the balance or imbalance of certain secretions, discharged in minute quantities into the blood by a set of glands which have no excretory ducts communicating with the external world; and upon disturbance of function of one or more of these glands depends a large group of unusual and hitherto unclassified diseases. Some vague notions of this doctrine were entertained or adumbrated in the past; but the true bearings of the theory of internal secretions were first grasped by Claude Bernard about the middle of the nineteenth century, and the main body of doctrine, as currently accepted, was developed during the first two decades of the twentieth century.

Of the five principal ductless glands, the pituitary was known to Galen, named by Vesalius (1543), described and called the hypophysis cerebri by Sömmerring (1778); the thyroid was vaguely described in the *De voce* of Galen, and more completely by Vesalius (Fabrica, 1543, lib. vi, cap. iv), Eustachius (1552) and Wharton (*Adenographia,* 1656), who gave it its present name; the thymus was known to the Greeks and described by Rufus of Ephesus; the suprarenals were described by Eustachius (1563), and named by Riolanus (1628); the parathyroids were

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discovered and described by Ivar Sandström in 1880, their anatomical and physiological independence established by A. Kohn, who called them the "epithelial bodies" (1899).

In the ensuing narrative, it is proposed to consider (I) the prehistory of the general doctrine of the internal secretions, (II) the descriptions of various diseases, which, as they came to be more generally known, served to focus and stress this doctrine in connection with (III) a long series of experiments on the physiology and physiological surgery of the ductless glands, which led to (IV) the gradual acceptance of the doctrine of the correlation of the internal secretions, in relation to metabolism, the functions of the autonomic nervous system, the physical, mental, and sexual status of the individual, and the hormonic equilibrium of the body.

I

The first to state clearly the function of the internal secretions of the ductless glands, was Théophile de Bordeu (1722-76), of Béarn (Basses Pyrénées), a graduate of Montpellier (1794), later a fashionable physician at the court of Louis XV, director of mineral baths in the Pyrénées, and founder of a now forgotten phase of vitalistic doctrine.

Fig. 1.—Théophile de Bordeu (1722-1776)

Bordeu appears to have been the first anatomist to employ the term "tissue"; his "Recherches sur le tissu muqueux ou l'organe cellulaire" (1767) immediately suggest the great Bichat, whom he influenced, it is true, but in a most untoward way. By *tissu muqueux,* which he also calls *l'organe cellulaire,* Bordeu means neither cellular structures, as Schleiden and Schwann saw them, nor protoplasm, as Purkinje and Schultze saw it, but simply such vague protoplasmic configurations as were visible through a lower power microscope. It was his ambition to confirm and uphold the humoral pathology of Hippocrates, and he regarded the three Hippocratic stages of disease, irritation, coction, and crisis, as dependent upon the glandular and other secretions. Corresponding with the different organs and secretions, he classified diseases, not

according to their clinical or pathological manifestations, but arbitrarily as cachexias, of which he devised a prodigious list, e. g., bilious, mucous, albuminous, fatty, splenic, seminal, urinary, stercoral, perspiratory; with an equally complex classification of the pulse as critical, noncritical, nasal, tracheal, gastric, renal, uterine, seminal, etc. All this undoubtedly influenced Bichat in the fundamental error of his scientific work, viz., the ascription of a specific vital property to each classifiable tissue. Bordeu's slender reputation to-day is concentered in a single idea—the doctrine that not only each gland, but each organ of the body, is the workshop of specific substance or secretion which passes into the blood, and that upon these secretions the physiological integration of the body, as a whole, depends. This doctrine is contained in his "Analyse médicinale du sang" (1776), the importance of which has been signalized by the eminent medical historian, Professor Max Neuburger, of Vienna. The book is a typical example of the purely theoretical reasoning so common in the medical literature of the eighteenth century, in which an intolerable deal of verbiage is spread over the smallest substructure of fact. Cases are frequently cited, but they are not true clinical delineations, only gossipy personal anecdotes, not unlike those of Brantôme. A great deal is said about the sexual side of man, and indeed the most interesting part of Bordeu's theory is his observation of the effects of the testicular and ovarian secretions upon the organism. He regarded the sexual secretions as giving "a male (or female) tonality" to the organism, "setting the seal upon the animalism of the individual," and as a special stimulus to the human machine (*novum quoddam impetum faciens*). He described in detail, the secondary sexual changes, not only in eunuchs and capons, but also in spayed animals of the female sex. In connecting all this with specific secretions, discharged, not externally, but into the blood, Bordeu was, as Neuburger rightly contends, very close upon the modern theory of the internal secretions, but, as he made no experiments, his ideas can only be regarded as an interesting phase of eighteenth century theorizing. Aside from Bordeu's deduction from what he saw, almost any stock-raiser or poultry fancier might have noted the same facts, and facts of equal moment had been noticed long before his time.

To begin with, one of the oldest therapeutic notions is the idea that such unsavory materials as the viscera or excreta of animals, administered either singly or as a *mixtum compositum,* might avail in the treatment of disease. This mode of therapy was a common feature of the Egyptian medical papyri, was known to the Greeks and Romans, made great headway during the dark ages, and reached its height in the seventeenth century. The four London Pharmacopeias of 1618, 1650, 1677, and 1721 abound with such remedies as the bile, blood, bones, brains, claws, eggs, excrement, eyes, fat, feathers, hearts, horns, intestines marrow, milk, omentum, placenta, rennet, sexual organs, skin, teeth, and

urine of all manner of animals; also bee glue, civet, cock's comb, coral, crayfish, earthworms, pearls, perspiration, saliva of a fasting man, scorpions, raw silk, silkworm's cocoons, moss from the skull of a man who has met a violent death, spermaceti, sponge, spider webs, cast off snake's skin, sea shells, swallows' nests, suet, viper's flesh, wax, and wood-lice; and along with these went those relics of the old Arabian polypharmacy, the theriacs and mithridates, which consisted of grand mixtures of anything and everything in the way of vegetable simples. In the seventeenth century there were actually "filth pharmacopeias" (*Dreckapotheken*).

The only physician of the time who did not attach much importance to these remedies was the one who had the greatest fund of practical sense, Thomas Sydenham. In the Pharmacopeias of 1721 and 1746 these nauseating remedies begin to disappear. One year before the latter date William Heberden, who was probably the greatest English clinician between Sydenham and Bright, published his satirical pamphlet "Antitheriaka" (1745), which was, in effect, a critical onslaught on polypharmacy. Heberden banished the theriacs and mithridates from medicine with the scholar's ironical smile, and with them went the filthier features of the materia medica. As a result of this cool douche of common sense, the Pharmacopeia of 1788 retains but a single animal remedy—wood-lice.

Now, while these things were the crude elements of the present day organotherapy, the theory upon which their employment was based was, in no sense, isotherapy or *similia similibus,* but simply the superstition of homeopathic or sympathetic magic (Frazer), as exemplified in such phases as the chthonian cult of the ancient Greeks or the medieval doctrine of signatures. In the ritual of the chthonian gods, or gods of the underworld, and the archaic pathology and neurology deriving from it, there existed, in the pre-Hippocratic period, a sacred pharmacopeia of animal and vegetable substances, sometimes the rejects of sacrifice (*catharmata*), and each drug (*φάρμακον*), in its function of averting, aborting, or driving out disease from the body, became a sacrificial scapegoat (*φαρμακός*), or substitute for the angered god, in the apotropaic, hilastic, and cathartic rites rendered to him. Here the viscera employed as remedies were not even identical with those affected by disease, but were used at haphazard, according to the tenets of a complex cult; e.g., the heart of an animal was employed in various diseases, but never in heart disease, the existence of which was even denied in some of the ancient writings. According to the medieval doctrine of signatures or similars, diseases or diseased organs were benefited by things similar to them; e.g., jaundice by the sight of a yellow bird, diseased lungs by the lungs of foxes, ear disease by the leaves of cyclamen, etc.; or, as Paracelsus put it, "heart cures heart, spleen spleen, lungs lungs." All this was abolished from therapy by Heberden's memorable exegesis. Before the time of Brown-Séquard, the

only animal extracts in our present pharmacopeia were the antispasmodics, musk and castoreum, which used to be described to gaping students, receiving their first instruction in the action of drugs upon the human frame, as derivatives of the preputial gland and follicles of the Thibetan musk deer and the beaver, respectively.

Another set of observations which bears upon our subject is that connected with the universal interest in giants and dwarfs, the acromegalics and achondroplasics of modern pathology. The acromegalic giants go back to the legendary lore of the Nephelim in Genesis (vi. 4), of Og, king of Bashan, the Anakim, Goliath of Gath, the Titans, Antæus, Polyphemus, Fafner and Fasolt, Gog and Magog, down to the huge images of Manchuria, the innumerable reports of excavations of giant skeletal remains, and the Irish, Chinese and Russian giants of more recent date. The achondroplasic dwarfs suggest the short limbed satyrs, the dwarf gods of Egypt (Bes, Phtah and others),[1] the black pygmy races,[2] the court dwarfs and buffoons figured by Velasquez and other great painters, and the athletic, acrobatic, and humoristic dwarfs of our vaudeville shows.

Fig. 2.—Paracelsus
(1493-1541)

Among the ancient Romans it was customary to test the increase in the girth of a young woman's neck, in connection with defloration or pregnancy, by measurement with a thread, as indicated in the lines of Catullus (lxiv, 371-378):

> Non illam nutrix orienti luce revisens
> Hesterno collum poterit circumdare filo;

but there is no evidence that they associated this cervical enlargement with the thyroid gland. Endemic goiter, however, was so well known in an-

[1] For a full account of these, with many illustrations, see the Munich dissertation of Franz Ballod.

[2] There are no white races of pygmies, and it is probable that most white dwarfs are myxedematous or achondroplasic.

tiquity that Juvenal (xiii., 162) has preserved its commonplace aspects in a single line: *"Quis tumidum guttur miratur in Alpibus"* ("Who wonders at goiter in the Alps?"); and Pliny, in his Natural History (xi., 68), hinted at one theory of its causation when he said that "only men and swine are subject to swellings in the throat, which are mostly caused by the noxious quality of the water they drink." In the sixteenth century Paracelsus found goiter to be endemic in the Salzburg region, again attributed it to metallic and mineral constituents in the water, and noticed that it coëxisted with another disease of the same locality, cretinism or myxedema. "While goiter is not a necessary characteristic of idiots (*proprium stultorum*)," says Paracelsus, "yet it is most commonly found among them (*so trifft es die am meisten*)," after which he wanders off into his usual astrological theories, in which few can follow him. The important point is that in goitrous regions, as Dock (*b*) (1909) says, cretins may have goiter or goitrous mothers, while the marriage of two cretins is usually sterile, which makes the observation of Paracelsus fit in very well with his main theory of the provenance of idiots (*generatio stultorum*). Long before the time of Paracelsus, the use of iodin, in the form of sponges and sea weeds, in the treatment of goiter, was taught by the Salernitan surgeon, Roger of Palermo (1180).

Fig. 3.—Felix Plater (1536-1614)

In 1614 Felix Plater, another Swiss physician, published an observation which, in connection with the doctrine of the "status thymico-lymphaticus," seems truly modern, an autopsy of a five months' infant, who had been suffocated by enlargement of the thymus gland (*mors thymica*).

As we begin to perceive the relation of these varied phenomena to the doctrine of internal secretions, it will not seem strange that Bordeu, who first stated the modern theory, should have hit upon the sexual gonads as the most obvious illustration, for nearly all these glands are in some way connected with the sexual characteristics of the individual. We may now pass from the stage of haphazard observations to that in which certain diseases were closely and accurately described, like objects in natural his-

tory. It is worth while to range these in chronological order, as illustrating the slow growth of a certain phase of inductive science.

II

On the continent of Europe, the disease "exophthalmic goiter" is variously known as "Basedow's disease," or *morbo di Flajani,* after the two observers who in Germany and Italy are thought to have originally described it. In 1840 Basedow, a physician of Merseburg, published a description (four cases) so complete that the Germans regard it as the classical one. The three symptoms which he signalized—swelling of the thyroid gland, protrusion of the eyeball, and palpitation of the heart—the Germans sometimes call the "Merseburg triad," which they also designate by the simple telegraphic epithet "Basedow." To this Charcot added a fourth cardinal symptom, the tremor. Among English-speaking people, following the nomenclature proposed by Trousseau, the disease is called exophthalmic goiter or Graves' disease, after the well-known Irish clinician who printed an accurate account of it in 1835. But, more than fifty years before Basedow, Caleb Hillier Parry, an eminent physician of Bath, England, made a notation of all phases of the Merseburg triad, part of which deserves citation, if only on account of its historic interest.

Fig. 4.—Carl Adolph Basedow (1799-1854)

"Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart.—The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1786. Six years before this period she caught cold in lying-in, and for a month suffered under a very acute rheumatic fever; subsequently to which she became subject to more or less of palpitation of the heart, very much augmented by bodily exercise, and gradually increasing in force and frequence till my attendance, when it was so vehement, that each systole of the heart shook the whole thorax. Her pulse was 156 in a minute, very full and hard, alike in both wrists, irregular as to strength, and intermitting at least once in six beats. She had no cough, tendency to fainting or blueness of the skin, but had twice or thrice been seized in the night with a sense of constriction and difficulty

of breathing, which was attended with a spitting of blood. She described herself also as having frequent and violent stitches of pain about the lower part of the sternum.

"About three months after lying-in, while she was suckling her child, a lump of about the size of a walnut was perceived on the right side of her neck. This continued to enlarge till the period of my attendance, when it occupied both sides of her neck, so as to have reached an enormous size, projecting forwards before the margin of the lower jaw. The part swelled was the thyroid gland. The carotid arteries on each side were greatly distended; the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress, especially on any muscular exertion, which I have rarely seen equalled. She suffered no pain in her head, but was frequently affected with giddiness. [After outlining his scheme of treatment, Parry concludes:] From this time no further application was made to me respecting this patient, who probably soon paid her debt to nature."

Between 1786 and 1815, Parry collected eight cases of this malady, which were published after his death, in 1825. He undoubtedly is entitled to the credit of the original and classical account of the disease, although he did not, as the French say, *afficher,* that is advertise his discovery by attempting to label it.

In 1802, Flajani published two cases of "bronchocele" or *gozzo,* in one of which he recognized two of the cardinal symptoms, the goiter and the cardiac palpitation. In discussing palpitation of the heart at the Meath Hospital in 1835, Robert Graves, the Dublin clinician, published his classical description of exophthalmic goiter, in which the exophthalmic feature was noted. He records that, in one patient, the beating of the heart could be heard at least four feet from her chest. Stokes, one of the greatest investigators of heart diseases, actually believed that the goiter was secondary to the cardiac affection. After the time of Graves and Basedow, many similar observations were collected by clinicians, but it was not until the year 1886 that the condition was attributed to an excessive outpouring of the thyroidal secretion by the German neurologist, Möbius, who at the same time described a number of related symptom groups, which he regarded as due to qualitative or quantitative changes in the secretion itself ("dysthyroidism"). The eye signs of exophthalmic goiter were localized by Basedow (1848), Albrecht von Graefe (1864), Stellwag and Dalrymple (1869), Möbius (1886) and others. The rapid emaciation attending the disease in spite of liberal diet was not understood until Friedrich Müller demonstrated that the combustion and tissue waste are due to vastly increased metabolism (1892). The value of iodin in the treatment of goiter, already known to the surgeons of Salerno, was demonstrated by J. B. Dumas and Charles Condet in 1820. The following names have been proposed for the disease (Dock (*a*), 1908): *Glotzaugen* (Basedow, 1840), *cachexie exophthalmique* (Charcot, 1856), *morbus Basedowi* (Hirsch, 1858; Charcot, 1859), exophthalmic goiter, Graves' disease (Trousseau, 1860), *morbo di Flajani* (Pensutti, 1857), Parry's disease (Osler, 1898).

In connection with the cretins observed by Paracelsus around Salzburg, it is of record that Curling, an English pathologist, first observed that absence of the thyroid body is accompanied by "symmetrical swell-

ings of fat tissue at the sides of the neck, connected with defective cerebral development" (1850). The classical account of this condition is due to Sir William Gull (1873). It was called myxedema by William M. Ord, of London, in 1877, on the ground that "the whole collection of symptoms are related as effects to jelly-like swelling of the connective tissue." The small size of the thyroid gland in myxedema was first emphasized by W. B. Hadden (1882). In 1902 F. Pineles (*a*) clearly differentiated the original endemic or familial cretinism associated with goiter (of Paracelsus) from sporadic cretinism (congenital myxedema).

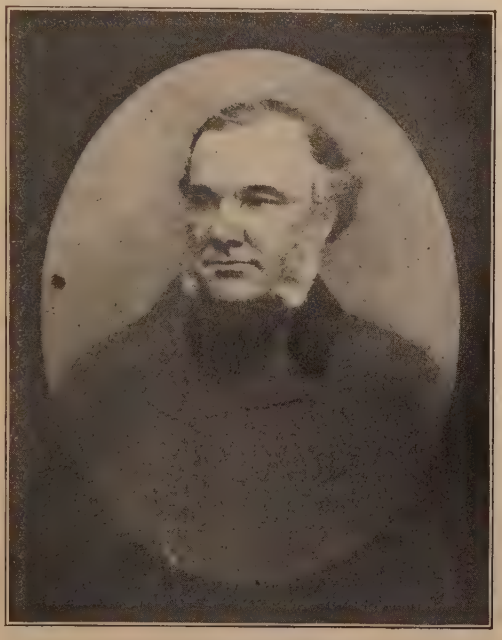


Fig. 5.—Thomas Addison (1793-1860)

It is a curious fact that the same volume of the journal in which Basedow published his account of exophthalmic goiter contains an observation by Bernhard Mohr (1840), a privat docent at Würzburg, of a remarkable and fatal obesity in a gardener's elderly wife, attended by incipient imbecility (*läppisches und kindisches Benehmen*), loss of memory, general somnolence, and scotoma, which, coming to autopsy, revealed a tumor-like degeneration of the pituitary body, produced by inmixture and copious effusion of a serous fluid, the discharge of which had induced pressure phenomena in reference to the adjacent parts of the brain. This was the first recorded case of what is now known as pituitary obesity, the "dystrophia adiposogenitalis" of Fröhlich (1901) and Frankl-Hochwart (1904).

The disease, tetany, now mainly associated with the parathyroid glands, and originally described by S. L. Steinheim (1830) and J. B. H. Dance (1831), was experimentally studied by Armand Trousseau in 1851 and named by Lucien Corvisart in 1852. The maternal and lactational tetany of Trousseau (*contractures des nourrices*) had already been noted by Steinheim and Dance. To Trousseau is due the diagnostic sign of spasm upon compression of the nerve trunks of a limb, and to Chvostek the facial spasm upon tapping the facial nerve.

In spite of the amount of original clinical delineation already on record in the first half of the nineteenth century, these lesions of the ductless glands attracted little attention. More interest was excited by the appear-

ance, in 1855, of what we must now regard as the principal milestone in the history of the subject, the monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," a quarto of forty-three pages by Thomas Addison, senior physician at Guy's Hospital, London. In the history of medicine, this work was destined to have an immortality of its own. In the very opening lines of his preface Addison clearly states, for the first time, the true paths by which, as subsequent experience has proved, the problems of these mysterious glandular structures have been best approached and attacked:

"If Pathology be to disease what Physiology is to health, it appears reasonable to conclude, that, in any given structure or organ, the laws of the former will be as fixed and significant as those of the latter; and that the peculiar characters of any structure or organ may be as certainly recognized in the phenomena of disease as in the phenomena of health. When investigating the pathology of the lungs I was led, by the results of inflammation affecting the lung tissue, to infer, contrary to general belief, that the lining of the air cells was not identical and continuous with that of the bronchi; and microscopic investigation has since demonstrated in a very striking manner the correctness of that inference—an inference, be it observed, drawn entirely from the indications furnished by pathology. Although pathology, therefore, as a branch of medical science, is necessarily founded on physiology, questions may nevertheless arise regarding the true character of a structure or organ, to which occasionally the pathologist may be able to return a more satisfactory and decisive reply than the physiologist—these two branches of medical knowledge being thus found mutually to advance and illustrate each other. Indeed, as regards the functions of individual organs, the mutual aids of these two branches of knowledge are probably much more nearly balanced than many may be disposed to admit; for, in estimating them, we are very apt to forget how large an amount of our present physiological knowledge respecting the functions of these organs has been the immediate result of casual observations made on the effects of disease. Most of the important organs of the body, however, are so amenable to direct observation and experiment, that in respect to them the modern physiologist may fairly lay claim to a large preponderance of importance, not only in establishing the solid foundation, but in raising and greatly strengthening the superstructure of a rational pathology."

Thus did Addison set forth the fact that Nature herself is sometimes the physiologist's best vivisector, even as Billroth and the followers of Marion Sims elucidated the pathology of the abdominal and pelvic viscera by making "autopsies *in vivo*."

On March 15, 1849, Addison read a paper before the South London Medical Society, in which he described the symptoms of what is now styled pernicious anemia, cases in which the whole surface of the body "bears some resemblance to a bad wax figure." Only three of the cases came to autopsy, but *"in all of them was found a diseased condition of the suprarenal capsules."* Was this a mere coincidence? Addison inquires.

"Making every allowance for the bias and prejudice inseparable from the hope or vanity of an original discovery, he confessed he felt it very difficult to be persuaded that it was so. On the contrary, he could not help entertaining a very strong impression that these hitherto mysterious bodies—the suprarenal capsules—may be either directly or indirectly concerned in sanguification; and that a diseased condition of them, functional or structural, may interfere with the proper elaboration of the body generally, or of the red particles more especially. . . . Indeed, not only had he found the anemia in question occasionally occurring in connection with purpura, but

had observed in cases of the latter disorder certain local symptoms, which pointed somewhat significantly to the suprarenal capsules; whilst the bloodless and waxy appearance of certain chlorotic females bore so close a resemblance to the anemia described that it was difficult not to suspect the existence of something common to both."

In his monograph of 1855, after referring to "an ill defined impression" that the suprarenals, in common with the spleen, thymus, and thyroid body, "in some way or other minister to the elaboration of the blood," and after a modest reference to the "curious facts" upon which he had "stumbled," Addison proceeds to develop the symptoms of what is now called Addison's disease—anemia, general languor and debility, feeble heart action, irritable stomach, with a dingy or smoky discoloration of the whole surface of the body, sometimes reaching a deep amber or chestnut brown—and elucidates its pathology in eleven cases, accompanied by striking and lifelike colored plates. From these records, which contain what Barker calls the "typical triad" of symptoms of Addison's disease (asthenia, disturbance of digestion, and melanoderma), it appears that the earliest known case was reported by his great colleague at Guy's, Richard Bright (of Bright's disease), in 1829. In another, reported by Addison himself, the post-mortem section was furnished "by my distinguished friend, Dr. Hodgkin" (of Hodgkin's disease). While developing his subject with the firm hand of the master in descriptive pathology, Addison draws no such striking conclusions in this memoir as we find in his paper of 1849, or as are indicated in the preface to the memoir itself. He does, however, draw attention to the important fact that even malignant disease may exist in both capsules without giving rise to the Addisonian discoloration of the skin. It was this memoir which led Brown-Séquard (*a*) to reproduce the fatal disease experimentally by excising the suprarenal capsules in animals (1856). The pouring out of the thyroidal and adrenal secretions during surgical shock or under the passion of fear (psychic shock) was emphasized long after by Walter B. Cannon (*a*) and George W. Crile.

In 1830 Johann Heinrich Kopp again drew attention to "asthma thymicum" and "thymus death" in childhood, already noted by Felix Plater. In 1889, Arnold Paltauf established the frequent combination of an enlarged thymus with hyperplasia of the lymphatic tissues, spleen, and bone marrow and aplasia of the cardiovascular system (status thymicolymphaticus) to which the status thymicus of Felix Plater, the status hypoplasticus of Julius Bartels (1908), the lymphatism of Heubner, the exudative diathesis of Adalbert Czerny, and the infantile arthritism of Comby are related. A classical study of the thymus gland was made by Alexander Friedleben in 1858.

There remains one other affection which, on account of its present importance, may be briefly considered, before passing to the experimental phases of the subject. The disease of acromegaly or gigantism was, as we

have said, regarded as an abnormity from the days of Goliath of Gath up to the time of John Hunter's famous and expensive chase after the skeleton of the Irish giant (1783); but even before this latter, definite cases had been reported, with good accounts of the deformities of the bones and the periodic coma, by Saucerotte (1772) and Noël (1779), and in the nineteenth century others were added by Alibert (1822), by Chalk (1857), by Friedreich in the case of the two Hagner brothers (1868), by Lombroso (1868), and by Sir Samuel Wilks, who in 1869 made a striking notation of the disease. The accepted classical account is that of Charcot's pupil, Pierre Marie, who differentiated the affection from myxedema, osteitis deformans, and leontiasis ossea, gave it its present name, and, four years later, correlated it with disease of the pituitary body. Marie's account was preceded by cases in which a lesion of the pituitary body in acromegaly had already been noted by Verga (1864), Brigidi (1877), and more particularly in the superb autopsy made by the late Edwin Klebs in 1884, which is the work of a veteran pathologist. This monograph, based upon a case furnished by Dr. Fritsche, of Glarus, Switzerland, contains two striking views of the patient and a remarkable diagram of the acromegalic skull; the hypertrophy of the pituitary body and the consequent widening of the sella turcica is strongly emphasized. But the opinion of the eminent pathologist is divided between this lesion and a proliferation of the thymus gland, which he found in the same autopsy, and after balancing the claims of the two lesions at length, he winds up by declaring that the cause of the disease must remain obscure. The view of Marie, which connects it directly with a lesion of the pituitary body,[3] has been, with some reservations, the theory accepted up to the present hour. It is interesting to note that, from the time of Galen up to the seventeenth century, the pituitary body was held to be the source of the mucous discharges of the nose. Vesalius, for this reason, called it the *"glans pituitam excipiens."* This idea was overthrown in Conrad Victor Schneider's treatise on the membranes of the nose ("De catarrhis," 1660) and by Richard Lower in 1672.[4] Théophile de Bordeu, in his anatomical researches, states that the ancients thought the office of the pituitary body was to empty its humors through the nostrils, the moderns holding that it sent them to the sinuses of the sella turcica, and there the matter ends with him, although he indulges a few vague conjectures as to the possibility of the passage of the pituitary secretions into the circulation.

[3] For an interesting account of this disease, see "Acromegaly, A Personal Experience" (London, 1912), by Leonard Portal Mark, a practicing physician, who has given a graphic and pathetic description of the gradual onset of the distressing malady in his own body. Although his disease was privately diagnosed by most of his clinical associates and he was "spotted" as an acromegalic in a Parisian crowd by Marie himself, Dr. Mark did not begin to realize his condition until he was fifty.

[4] The work of Schneider and Lower did away with the innumerable recipes for "purging the brain" of these alleged pituitary humors.

III

In the first half of the nineteenth century the accepted view of the phenomena of secretion was that enunciated by Johannes Müller, viz., that the process consists of two phases—secretion proper, or the casting out of substances upon a surface inside the body, as in the case of the gastric juice; and "excretion," or the voiding of such secreted substances into the external world, as in the case of bile or urea. This distinction was somewhat artificial, since bile, urea, and other excreted substances are also secretions in the first instance. In 1801 the French physiologist Legallois, as Gley has noted, surmised, from the identity in composition of all varieties of arterial blood and the diversity of venous blood in different parts of the body, that this diversity is acquired, in each case, from the loss of some substance to the organ from which the vein proceeds. Thus, Bordeu's idea, A (arterial blood) $= S$ (secretion) $+ V$ (venous blood), and Legallois' idea, V (venous blood) $= A$ (arterial blood) $- S$ (secretion), are identical. When A and S are chemically known, A being constant, V will be known; or, when A and V are known, S will be known. V is always a variable. This remarkable intuition of Legallois, like the hypothesis of Bordeu, remained on a theoretical basis and was not put to experimental proof. In 1849 A. A. Berthold, a Göttingen professor, is said to have transplanted the testes of a fowl to another part of its body, with complete retention of its sexual characters, a phenomenon which he inferred to be due to "the productive relation of the testes, i.e., to its effect upon the blood and thence, through the corresponding effect of such blood, upon the entire organism." This experiment and the *aperçu* drawn from it are of paramount importance, but Berthold's paper exerted no sensible effect upon the physiology of his period. Nevertheless, the ductless glands were coming to be known among the German physiologists as "blood vessel glands" (*Blutgefässdrüsen*) or "blood glands" (*Blutdrüsen*), and were regarded by the histologists Henle and Kölliker as preparers of different chemical substances, which are utilized by the organism through the blood.

Fig. 6.—Arnold Adolph Berthold (1803-1861)

Beyond this general theory, which is identical with Bordeu's, no special function could be assigned to the different ductless glands. Even Henle asserted that these glands have no influence whatever upon animal life, that they can be extirpated or undergo pathological degeneration without affecting either the sensory or motor functions of the body. The path breaking importance of Addison's great monograph on the effect of disease of the suprarenal capsules may be thrown into relief by citing Hyrtl's witticism about the suprarenal—that the unknown nature of its functions insures it from bothersome investigation at the hands of medical men (*"Die unbekannte Funktion der Nebenniere sichert dieses Organ von lästigen Nachfragen in der Heilwissenschaft"*).

If we regard the lungs or the individual cells of the body tissues provisionally as ductless glands, then it will be perceived that the truth of the equation formulated by Legallois had already been demonstrated quantitatively when Lavoisier proved that inspired air is converted into carbon dioxid and water, and when Lagrange, through his pupil Hassenfratz, proved that the oxygen in inspired air, being dissolved in the blood, takes up carbon and hydrogen from the body tissues as the blood courses through them (1791). We now know that the respiratory center in the medulla is stimulated by the CO_2 in the venous blood, which Lavoisier and Lagrange had shown to be, in effect, a true metabolite, or waste product of tissue oxidation. Their work was, in fact, the starting point of the chemical study of metabolism, which received its next great advancement in Claude Bernard's study of glycogen; for, although the latter may not be, in the strict sense, a true internal secretion, discharged from a gland into the blood, yet its investigation led Bernard (*d*) to the classical statement of the doctrine of internal secretions as such:

> "In animals the glycogenic secretion is an internal secretion because it is discharged directly into the blood. I have considered the liver, as found in the higher vertebrates, as an organ with a double secretory function. It seems to reunite, in effect, two distinct secretory elements, and it represents two secretions, one external, the biliary secretion, the other internal, the glycogenic secretion, which is discharged into the blood."

In the year 1843 Claude Bernard, in his graduating thesis, made the discovery that cane sugar is acted upon by the gastric juice, being converted by it into dextrose. This experimental fact led to a train of reasoning, which was to revolutionize the physiology of nutrition and metabolism and at the same time to introduce the new concept of internal secretions, and to be the starting point of the experimental production of disease by the artificial use of chemical and physical agencies. All carbohydrates, Bernard reasoned, must get into the blood in the form of dextrose. "What becomes of this dextrose?" he next inquired. Somewhere between the alimentary canal (*via* the portal vein) and the liver, between the liver (*via* the right heart) and the lungs, between the lungs (*via* the left heart) and the various body tissues, this dextrose is either destroyed and disappears or is trans-

formed into some other substance. If the locus of this transformation could be discovered and its activities inhibited, an artificial diabetes might be produced by the induction of excess of sugar in the blood. On feeding a dog on rich sugar diet and killing it at the height of digestion, he found the hepatic veins loaded with dextrose, and although this looked at first as if the liver was not the site of transformation, Bernard (*a*) changed his mind when he found that the blood from the hepatic vein of another dog fed upon meat only (a sheep's head) was also loaded with grape sugar. Thus, it appeared that the liver is a sugar manufacturing plant, and that its sugar producing or glycogenic function is in the nature of an internal secretion, a view which he confirmed by many varied experiments, publishing his results in 1848-50. About the same time Bernard discovered that a puncture in the region of the fourth ventricle of the brain in the dog will produce a temporary glycosuria (1849) or medullary diabetes mellitus. The later experiments of E. Frank (1912) and of Harvey Cushing (*d*) and his associates (1913) indicate that there is also a polydipsia and polyuria deriving from the pituitary body. As a simple decoction of the liver substance was always found to contain dextrose, the next step was to ascertain how the liver produced this substance at the expense of the materials sent from the alimentary canal. After perfusing a freshly excised liver until the wash water from the hepatic vein contained no sugar, Bernard found that, if the liver were left in a warm place for a few hours, a subsequent perfusion would once more come out loaded with sugar, and, although this property of the hepatic tissue could be destroyed by boiling, the sugar producing power could be restored by adding to a decoction of the boiled liver a small quantity of fresh liver infusion. From this he inferred that the glycogenic function is, in effect, a fermentative process, and that its agency is a kind of starch. In 1855, he succeeded in obtaining this glycogenic substance in the form of a dry powder, which could be converted into dextrose by fermentation, although it did not itself respond to the sugar tests. In 1857, by his potash-alcohol process, Bernard (*c*) obtained it in the pure state as "glycogen." In Bernard's view, glycogen was the *"sécrétion interne"* of the liver, over and above its ordinary external secretion, bile. It was the fact that glycogen could be seen, touched, tasted and experimented upon,

Fig. 7.—Claude Bernard (1813-1878)

as such, that established the theory of internal secretions as a working principle in physiology. The epoch-making character of Bernard's discovery is best indicated in the language of Sir Michael Foster, who has given the most fascinating appreciation of his work in medical literature:

"The view that the animal body, in contrast to the plant, could not construct, could only destroy, has, as we have seen, already being shaken. But evidence, however strong, offered in the form of statistical calculations, of numerical comparisons between income and output, failed to produce anything like the conviction which was brought home to every one by the demonstration that a substance was actually formed within the animal body and by the exhibition of the substance so formed.

"No less revolutionary was the demonstration that the liver had other things to do in the animal economy besides secreting bile. This, at one blow, destroyed the then dominant conception that the animal body was to be regarded as a bundle of organs, each with its appropriate function, a conception which did much to narrow inquiry, since, when a suitable function had once been assigned to an organ, there seemed no need for further investigation. Physiology, expounded, as it often was at that time, in the light of such a conception, was apt to leave in the mind of the hearer the view that what remained to be done consisted chiefly in determining the use of organs such as the spleen, to which as yet no definite function had been allotted. The discovery of the glycogenic function of the liver struck a heavy blow at the whole theory of functions.

"No less pregnant of future discoveries was the idea suggested by this newly found out action of the hepatic tissue, the idea happily formulated by Bernard as "internal secretion." No part of physiology is at the present day being more fruitfully studied than that which deals with the changes which the blood undergoes as it sweeps through the several tissues, changes by the careful adaptation of which what we call the health of the body is secured, changes the failure or discordance of which entails disease. The study of these internal secretions constitutes a path of inquiry which has already been trod with conspicuous success and which promises to lead to untold discoveries of the greatest moment; the gate to this path was opened by Bernard's work."

In 1856, one year before Claude Bernard obtained glycogen in the pure state, the doctrine of internal secretions was put upon a firmer basis through the important experiments of Brown-Séquard and Moritz Schiff (*a*). Only a year after the publication of Addison's great monograph on suprarenal disease, Brown-Séquard (*a*) succeeded in producing an exaggerated form of Addison's disease in different animals by removal of the suprarenal capsules, the symptoms being the same and the result of the experiment being rapidly and invariably fatal (1856). If only one capsule were removed, there was no appreciable change in the normal animal, but death would rapidly supervene upon removal, even after a long interval of time, of the other capsule. Furthermore, Brown-Séquard found that a transfusion of normal blood into the veins of an animal deprived of its suprarenal capsules will prevent its death for a considerable time, indicating that the normal suprarenal capsules secrete a material which is necessary for the maintenance of life.

In the same year (1856), Moritz Schiff, of Frankfort on the Main, found that excision of the thyroid gland in dogs is invariably fatal. His results were forgotten for over twenty-five years, when, following the description of myxedema by Gull (1873) and Ord (1878) and the first excision of the thyroid gland for goiter by the Swiss surgeon, Theodor Kocher (*a*) (1878), J. L. Reverdin of Geneva showed that an "operative myxe-

dema" is produced in man by complete excision of the thyroid (1882). This was confirmed by Kocher (*b*), who found that total thyroidectomy is followed by a "cachexia strumipriva" or "cachexia thyreopriva" (1883). Hereupon Schiff (*b*) returned to the charge and, in 1884, published the results of 60 thyroidectomies in dogs, all fatal, with such significant symptoms as tremor, spasms, and convulsions. What is more to the purpose, Schiff demonstrated that these symptoms could be prevented by a previous graft of a portion of the thyroid gland beneath the skin or into the peritoneal cavity of the animal, or by the injection of thyroid juice into a vein or under the skin, or by the ingestion of thyroid juice or raw thyroid by the mouth. These experiments, which were confirmed by Horsley, von Eiselsberg, and a host of other observers, led in time to the remarkably successful treatment of myxedema by means of thyroid extract. In 1800, Pinsuti proposed administration of the thyroid juice, which was tried out on dogs by Vassale and Gley in 1891. In the same year G. R. Murray (*a*) (*b*), of London, showed that myxedema can be prevented by subcutaneous injections of thyroid juice. In 1892, Sir Hector MacKenzie (*a*) (*b*) (London) and Frantz Howitz (Copenhagen) demonstrated the efficacy of oral ingestion of the dried thyroid gland in myxedema, which was immediately taken up in the clinics and soon became established in general practice. In 1884, Sir Victor Horsley (*a*) produced an experimental myxedema by removal of the thyroid in monkeys, which were found to survive much longer than dogs. It was also found by Allara (1885), Eward (1890), and others, that experimental thyroidectomy is negative in birds, rodents, and herbivorous animals, and that, both in animals and man, operative myxedema is produced less frequently as age advances. In 1888, Sir Felix Semon, in an important collective investigation, maintained that etiologically cretinism, myxedema and operative myxedema (cachexia thyropriva) are one and the same, although clinically the congenital, idiopathic, and operative myxedemas, endemic and sporadic cretinism, as well as dwarfism, mongolism,

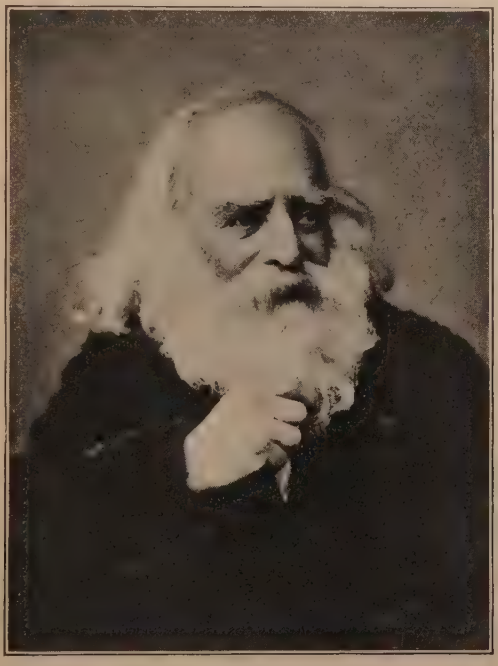


Fig. 8.—Moritz Schiff (1823-1896)

and achondroplasia not associated with thyroid insufficiency, are now sharply differentiated from one another. In 1889, Brown-Séquard, then aged seventy-two, found himself vastly rejuvenated as to general health, muscular power, and mental activity by the subcutaneous injection of testicular extracts, the active principle of which Pöhl, the Russian physiologist, holds to be the substance spermin ($C_5H_{14}N_2$).

These experiments of Brown-Séquard easily lent themselves to ridicule, but he followed them up, even to the extent of giving pituitary extract for disease of that organ (1893), and it was his work upon these extracts which led him to formulate the following statement of the old Bordeu theory of internal secretions:

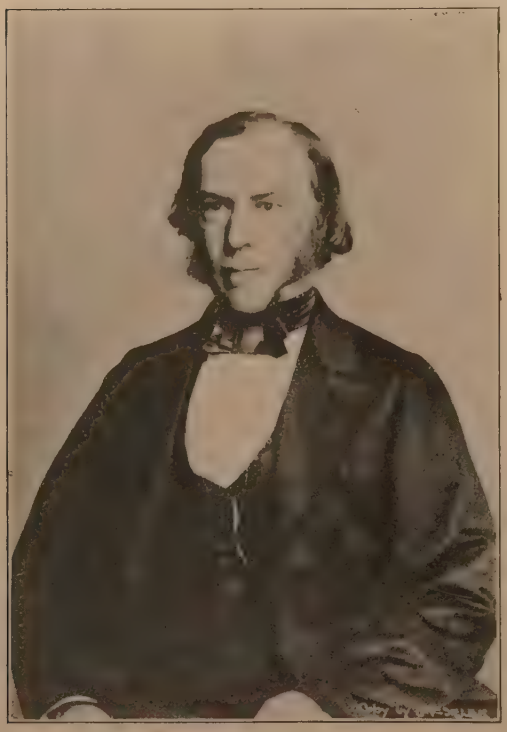


Fig. 9.—Charles-Édouard Brown-Séquard (1817-1894)

"All the tissues, in our view, are modifiers of the blood by means of an internal secretion taken from them by the venous blood. From this we are forced to the conclusion that, if subcutaneous injections of the liquids drawn from these tissues are ineffectual, then we should inject some of the venous blood supplying these parts. . . . We admit that each tissue and, more generally, each cell of the organism secretes on its own account certain products or special ferments, which, through this medium, influence all other cells of the body, a definite solidarity being thus established among all the cells through a mechanism other than the nervous system. . . . All the tissues (glands or other organs) have thus a special internal secretion and so give to the blood something more than the waste products of metabolism. The internal secretions whether by direct favorable influence, or whether through the hindrances of deleterious processes, seem to be of great utility in maintaining the organism in its normal state."

As theory goes, nothing new has been added to the doctrine of internal secretions since Brown-Séquard stated it in this form in 1891. In his essay on "Variation" (1868) Darwin seems to have had a glimmering of the idea, when he stated that gemmules are transported from all parts of the body to the ovum to insure their reproduction (pangenesis), and the Bayliss-Starling doctrine of the "hormones" or chemical messengers, as we shall see, is not essentially different from that of Bordeu and Brown-Séquard.

From the time of Brown-Séquard on, experimental investigation of the subject moved so rapidly and in so many different directions that the general trend of the theory became obscured or lost in the details of controversy. And further obfuscation was brought about by the constant succession of dissolving views of the subject of carbohydrate metabolism. In 1886, Joseph von Mering produced an experimental diabetes by the ingestion of phlorizin. In 1889, J. von Mering and Oscar Minkowski obtained diabetes by an experimental excision of the pancreas. The histological, pathological and clinical studies of E. L. Opie (1901), L. V. Ssobolew (1902), and W. G. MacCallum (1909) indicate that the source of this pancreatic glycosuria is to be found in a specialized group of cells, called the islands of Langerhans. Thus, it would appear that the pancreas possesses an internal secretion as well as a digestive function.

Fig. 10.—Joseph von Mering (1849-)

Fig. 11.—Oscar Minkowski (1858-)

The discovery of iodothyrin in the body of Eugen Baumann (*b*) in 1896 suggested the relation of the thyroid gland to iodin metabolism and an adjoining pair of ductless glands, the parathyroids, discovered by the Swedish anatomist, Ivar Sandström, in 1880, would appear, from experiment, to have an influence on calcium metabolism. In his thyroidectomies of 1856, Schiff (*b*) noted

tetany in some cases, but did not associate this with the parathyroid. The occurrence of tetany after total excision of the thyroid had been a matter of ordinary observation in Billroth's clinic (1880). In 1891, Eugène Gley showed that, where excision of the thyroid is negative in certain animals, these animals will speedily die if the four parathyroids are also removed. The physiological effects of excision of the parathyroid were further investigated by Giulio Vassale and Francesco Generali in 1896. In 1892, the Viennese surgeon Anton von Eiselsberg (*a*) made a successful transplantation of the parathyroid glands from the neck to the abdominal wall in a cat, and showed that tetany may be produced upon its removal from this site. Subsequent experiments by H. Leischner (1907) and by W. S. Halsted (*a*) (*b*) (*c*) at the Johns Hopkins (1909) showed that the production of tetany after thyroidectomy is really due to removal of the closely adjacent parathyroids, the tetania parathyropriva of Erdheim. These observers found, as in Schiff's experiments, that the tetanoid spasms will be abolished upon injection of an extract of the gland or after parathyroid feeding or upon regrafting the gland itself. In 1908, W. G. MacCallum and C. Voegtlin (*a*) showed, at the Johns Hopkins Hospital, that tetany may be abolished by treatment of the patient with calcium salts. All these experiments tend to identify operative tetany with idiopathic tetany and to demonstrate the relation of both to parathyroid insufficiency. Another ductless gland, the pituitary body, has been shown to have a marked relation to carbohydrate metabolism, and, like the suprarenal and parathyroids, to be essential to the maintenance of life.

The pituitary body, which the anatomist Sömmerring called the hypophysis cerebri (1778), was, as we have seen, regarded as an organ discharging a mucous secretion into the nostrils, until this theory was disproved in the seventeenth century. This structure consists of an anterior glandular lobe (*pars glandularis*) and a smaller posterior lobe, including the *pars nervosa,* or neurohypophysis, made up chiefly of neuroglia and derived from the nervous system; and of the *pars intermedia* of Herring, a thin epithelial covering, from which pituitrin, the active principle of the internal secretion of the gland is, in all probability, derived. The gland is connected with the floor of the third ventricle of the brain by means of a stalk or infundibulum. In 1838, the embryologist, H. Rathke, showed that the anterior lobe is developed by the protrusion of an ectodermal pouch (Rathke's pouch) from the roof of the pharynx, and is made up of epithelium derived from the buccal cavity. It lies in the embryonic rest of Rathke's pouch "as a ball is held in a catcher's mitten" (Cushing). The posterior lobe, made up of nervous tissue, is derived from a corresponding prolongation from the anterior cerebral vesicle. Until recently the pituitary body has been inaccessible to surgeons and to physiological experimenters, by reason of its encasement in the sella turcica of the sphenoid bone. Experimental removal of the pituitary (hypophysectomy) was

essayed by Sir Victor Horsley (*b*) (1886), Marinesco (1892), Vassale and Secchi (1892–94), Gatta (1896), Biedl (1897), von Cyon (1898–1900), and others, with negative or contradictory findings, resulting, no doubt, from the difficulties encountered in approaching the gland through the skull and of insuring its entire removal under these conditions. In 1908, an important advance was made by Nicholas Paulesco, of Bucharest, who devised an operation by the temporal route and showed that the pituitary body is essential to life, its removal being fatal to the animal. At the same time he found that removal of the anterior lobe is equivalent to entire removal and that excision of the posterior lobe is negative. Paulesco's experiments were put to the test by Harvey Cushing and his associates at the Johns Hopkins Hospital, their experiments being performed mainly upon dogs. They found that total removal or removal of the anterior lobe alone are alike fatal, the animal dying in three days with a peculiar train of symptoms consisting of lowered temperature and blood pressure, sluggishness, unsteady gait, rapid emaciation, slowing of pulse and respiration, diarrhea, diminished urine in adults, polyuria and glycosuria in puppies. Partial removal of the anterior lobe in normal dogs was found to produce a pronounced state of obesity, with a remarkable shrinkage of the external (male) genitalia. In other words, Cushing produced, by experiment, a genuine pathological reversion to the condition known as obesity with genital infantilism, hypopituitarism, or "dystrophia adiposogenitalis," described by Alfred Fröhlich in 1901. The neighborhood symptoms in this condition, referred to the eye, were later described by Cushing (*a*) in 1906. In the case of the posterior lobe, which, as shown by Cushing and Goetsch, discharges its secretion into the cerebrospinal fluid, partial removal or the production of insufficiency of the secretion by putting a clip upon the stalk of the gland produces, at first, a temporary lowering of the animal's assimilation limit for sugars, followed by a marked and permanent increase in its tolerance for carbohydrates, which is again promptly lowered by injection of an extract of the posterior lobe. In 1895,

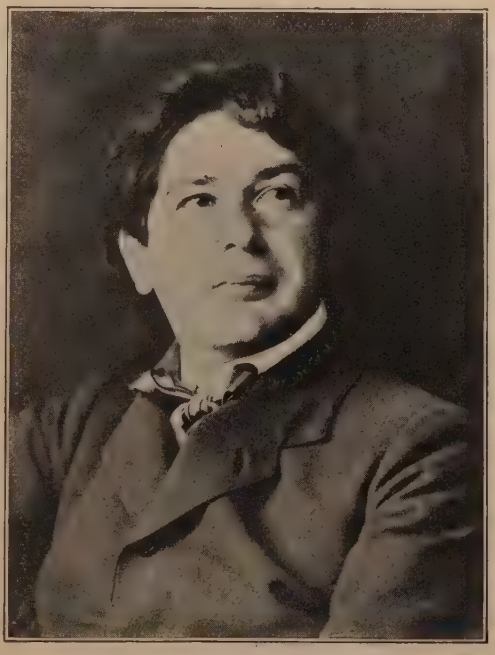


Fig. 12.—Alfred Fröhlich

Oliver and Schäfer (*a*) found that the mammalian pituitary possesses an active principle which, upon injection, elevates the blood pressure and increases the force of the heart beat. In 1898, Professor William H. Howell, of the Johns Hopkins University, showed that this property is possessed by the extract of the posterior lobe (*pars intermedia*) alone. This extract (pituitrin) has a specific action upon the smooth muscle of the uterus and bowel, whence its use in obstetrics (uterine atony) and in postoperative intestinal paresis. It is of distinct value in hypopituitary states. In his Harvey Lecture of December 10, 1910, Cushing introduced the pathological idea of "dyspituitarism," or perverted function of the gland, as a generic concept, covering excess or insufficiency of its function, and for the following reasons. In accordance with the clinical and pathological findings of Parry, Graves, and Basedow, exophthalmic goiter was regarded as a state of "hyperthyroidism" or excessive secretion of the gland, while the myxedema of Curling, Gull, and Ord was termed "hypothyroidism" (diminished secretion or insufficiency). But it was found that in many cases the two conditions may be blended, as Paracelsus had originally surmised in the Salzburg region, producing an overlapping of the cardinal symptoms of either. For this reason the term "dysthyroidism" was proposed by Marie for both. In like manner, states of overactivity in the pituitary (hyperpituitarism), associated with overactivity of the sexual glands, or of underactivity (hypopituitarism), associated with genital aplasia and sexual inactivity, may be superimposed one upon the other, making the term "dyspituitarism" more appropriate in the majority of cases. As a goitrous mother may have a cretinous infant, a big, bony acromegalic woman, as originally observed by Crookshank and confirmed by Cushing, may have a son afflicted with pituitary infantilism or obesity. Cushing (*d*) has also shown that there is evidence of pituitary activity in pregnancy and hibernation (1912), and his experiments upon its relationship to the sympathetic nervous system (1913) have led him to the conclusion that a lesion of the posterior lobe (*pars intermedia*) may cause the increase of normal urine (polyuria), otherwise known as diabetes insipidus. Finally, he has devised a standard surgical procedure for approaching the almost inaccessible pituitary gland, which was first operated upon in man with success by H. Schloffer in 1907. Physiological or Hunterian surgery, which had almost fallen into abeyance until the twentieth century, has been the principal means of elucidating the obscure physiology of the ductless glands.

In this connection, it is interesting to note that the first experiment in physiological surgery upon human beings was performed by the gynecologist, Robert Battey, of Georgia, who, on August 27, 1872, excised the normal ovaries for the relief of a neurotic condition. The physiological basis of this operation, a supposed internal secretion from a specialized set of interstitial ovarian cells, has been indicated in many ways. A Battey's operation upon women who have not attained the menopause will produce

an artificial change of life. Ovariotomy has been found in some cases to have a beneficial effect upon osteomalacia in women. Glass (1899), Morris (1901), Marshall and Jolly (1905) have shown that grafting or transplantation of the ovaries in previously ovariotomized women will reëstablish menstruation, sexual desire, and general well being. Eunuchoidism and the effects of castration upon the male and female organism have been investigated in detail by J. Tandler and S. Grosz (1907-10). The experiments of Lane-Claypon and Starling (1906) demonstrated that the inhibitory effect upon pregnancy and lactation of a Battey's operation in rabbits will not be produced by section of the mammary nerves or of the spinal cord. Similarly, the experiments of Brown-Séquard and Pöhl on spermin and the fact that ligation of the vas deferens in young animals will abolish the power of reproduction, while permitting full development of the sexual characters and the sexual appetite, go to show that the sexual gonads in the male have an internal secretion, which is supposed to arise from the interstitial cells of Leydig in the seminal tubules.

Fig. 13.—Robert Battey (1828-1895)

The pineal gland, or epiphysis cerebri, known to Galen (*De usu partium,* viii, 3) and the Greeks as the conarium (κωνάριον), was regarded by Descartes as the seat of the soul, and by later naturalists as a vestigial eye in certain animals. As this gland undergoes involution at puberty, pathological evidence has been sought to prove that the function of the pineal secretion is to inhibit overripening of the organism, particularly overdevelopment of the gonads and the sexual system. In 1898, the pediatrist Heubner described a case of precocious sexual and somatic development in a boy of four and one-half years, which, coming to autopsy, revealed a teratoma of the pineal. In 1907, Marburg (*a*) (*b*) had collected forty such cases, from which he sought to establish the doctrine of "macrogenitosomia precox" from pineal dysfunction (hypopinealism), characterized by pressure and neighborhood symptoms referred to the eye and cerebellum, with precocious sexual, somatic, and mental maturity. Frankl-Hochwart maintained that this syndrome connotes a pineal tumor. Of seventy cases since collected (all but two in boys), only twenty-five occurred before puberty, and many of these had no signs of precocious development. Experimental surgery of the organ was difficult and consequently fatal

(although the gland is not essential to life) until W. E. Dandy devised a viable operative approach to the gland (1915). The experimental extirpations of Dandy, as also those of Exner and Böse (1900-11), negative the Marburg postulate of hypopinealism, while the pinealectomies of Sarteschi (1910-13), Foà (1912-14), and Horrax (1916) confirm it. Feeding and injection experiments by C. L. Dana and W. N. Berkeley (1913-14), and later those of C. P. McCord (*b*) (1914-15), show that the precocity of development attributed to pineal deficiency is also obtained by adding pineal substance to the blood, the effect ceasing when maximum growth (short of giantism) is attained. In the view of McCord (*c*), the pineal gland contains a substance that stimulates growth and development, but dyspinealism, if existent, is probably overlapped by pluriglandular involvement. Hoskins' (*a*) feeding experiments, with the different ductless glands, show that the effect of any of the glands upon growth rate is variable and inconstant.

In 1905, Joseph Halban (*b*) advanced the theory that an internal secretion of the placenta may cause hyperplasia of the breasts and uterus, independently of the ovaries. This action has since been confirmed for placental extract in ovariotomized animals, and in the absence of the thyroids, adrenals, or pancreas. The chemical hormone, if existent, has not been isolated, but is identical in action with the corpus luteum (Frank).

In 1904, J. Wiesel (*a*) first described the so-called chromaphil system, i.e., the tissues having a strong affinity for the chromium salts of staining reagents, notably the medulla of the suprarenal glands, the paraganglia and similar tissues in the sympathetic ganglia, the carotid gland, the chromaffin body of the plexus ganglia, and the accessory body (*Nebenkörper*) of Zuckerkandl. This system is to be distinguished from the interrenal system or capsule of the adrenal body. All chromaphil tissues deriving from sympathetic nerve cells produce epinephrin and distribute it to the blood channels. Epinephrin, or suprarenal extract, was first isolated by G. Oliver and Sir E. S. Schäfer (*b*) in 1894-95. Its varied effects upon the system, such as upon the blood pressure, upon the blood supply of muscle and the sugar supply of blood (W. B. Cannon) illustrate the multiplex functions of the ductless glands. Epinephrin, the chromaffin substance, was isolated by S. Fränkel (1896) and investigated by O. von Fürth (1897-98), J. J. Abel (1898-1904), and J. Takamine (1901). In 1895, P. Star first noted the persistency of the thymus in Addison's disease, the inference being that the normal involution of the gland is due to insufficiency of epinephrin in the blood. Underfunction of the chromaffin system, characterized by diminished supply of epinephrin in the blood, therefore, produces Addison's disease, or status thymico-lymphaticus. Overfunction, with excess of epinephrin in the blood, while rare, is believed to occur in contracted kidney, atherosclerosis of the arterioles, and Graves' disease.[5]

[5] The observation that epinephrin hypertension is attainable only with dosages that paralyze the gastro-intestinal tract would seem to indicate that the assumed condition is not compatible with life.—R. G. H.

Overfunction of the interrenal system (cortex of the suprarenal gland) produces changes in the sexual gonads, with such conditions as pseudohermaphroditism, precocious puberty, suprarenal virilism, and hirsutism.

In disturbances of the endocrine functions of the sexual gonads, hypergenitalism and hypogenitalism may be independent of or associated with disease of the pituitary, adrenals, or pineal glands, or with the "pluriglandular syndromes" in which more than one are involved. The concept "pluriglandular insufficiency" was introduced by Claude and Gougerot (1907-08). Sexual infantilism without obesity presents two types, the typus Lorain (1871), with small consumptive looking body and delicate limbs, and the myxinfantile or myxedematous type (typus Brissaud (*a*) (*b*), 1897). The pluriglandular syndromes are usually characterized by loss of sexual characteristics, impotence, neurasthenia, and by those remarkable changes in the conformation and expression of the facies which are familiar in acromegaly, goiter, and myxedema. Thus, in a pluriglandular syndrome, well described by Walter Timme in 1918, the clinical picture, characterized by muscular fatigability, sexual infantilism or abnormity, low blood pressure and blood sugar, and Sergent's white line of adrenal insufficiency, is at first dominated by the enlarged thymus and latterly by pituitary hyperplasia, with marked acromegalic symptoms.

Perhaps the most interesting feature of the ductless glands is just this correlation with the sexual function. Aside from the other correlations, diminished sexual power is common to the two main groups of pituitary disorders, acromegaly and sexual obesity with infantilism, although, in acromegaly, sexual frigidity is not necessarily common to the initial or transition stage, but usually comes on after the hyperpituitary stage has been succeeded by dyspituitarism or hypopituitarism (L. F. Barker). The well defined acromegalic has been likened to the Neanderthal man, who was probably, as the gorillas are, hyperpituitary (Keith), to eunuchs, who are excessively tall when not overcorpulent, and to the tall, raw boned, heavy jawed peoples of the northern countries, who are often sexually cold. The obese infantile patients of the Fröhlich type, on the other hand, suggest the fat boys of the Pickwick Papers and the large hotels, and the eunuchoid "Lobengulas" described by Sir Jonathan Hutchinson. Even in folklore, obesity connotes sexual frigidity. In a recent view of Dr. Leonard Guthrie, the autopsy of the great Napoleon at St. Helena indicates that the corpulence of his later years, his gradual loss of intellectual keenness, his general fat-headedness from the time of the Russian campaign, may have been due to the onset of a pituitary obesity, the dystrophia adiposogenitalis of Mohr and Fröhlich. In Frank Harris' recent life of Oscar Wilde (New York, 1920), Bernard Shaw suggests that Wilde's homosexualism may have been associated with latent acromegaly, as indicated by his large flabby physique and heavy features. The logical opposites of acromegalics are, therefore, not the fat patients of the Mohr-Fröh-

lich type, but the short, swarthy, goat-legged achondroplasics who often exhibit great muscular strength, unusual sexual precocity, and general salacity, or the dark skinned people of the suprarenal type. These have been assimilated to the satyrs of mythology, to the short, swarthy, troglodyte peoples, such as the Iberians, or the Euskarians, the primitive inhabitants of Britain, to "the short-limbed children, of precocious sexuality," and particularly the "forward female children, with full busts, already boasting of their affairs," who are so common on the streets of modern cities. It was not without reason that the Greeks represented the great god Pan as a goatish individual. Except in the negro, the generic sexual type, the differential characters of which are harped upon even in the plays of Dumas *fils,* is short, swarthy, muscular; the frigid type, of high pituitary index, is either flabby and obese (the *kühle Blonde* of the Germans) or the lank, raw-boned acromegalic. It is said that many achondroplasic dwarfs of history, like Sir Geoffrey Hudson, were of the salacious type. The records of the obstetric clinics show that female achondroplasics, married or unmarried, have sometimes undergone the operation of Cesarean section three or four times running. The amazing fertility of achondroplasic women has been emphasized in the statistical or biometrical investigations of Karl Pearson, and that this type connotes extreme sexuality is borne out by the observations of Pierre Marie and his coworkers at the Salpêtrière. Crookshank maintains that "the Bengalee is pretty much in the same state as a sufferer from a *forme fruste* of exophthalmic goiter; while the pigmentation and genital gigantism of the negro are suggestive of adrenal assertion." He further points out that "certain genital malformations or abnormities are almost always accompanied by adrenal tumors"; and Iscovesco has stated that adrenal lipoids, when administered hypodermically, rapidly produce genital overgrowth.

Sir Arthur Keith has recently sought to explain the differentiation of anthropoid apes and of ethnic types in man in the light of endocrine doctrine. The Caucasian and the Malay, akin to the orang, show the predominance of hyperpituitarism, the negro and the Mongol, akin to the gorilla, of hyperadrenalism and hyperthyroidism, respectively.

IV

The most remarkable fact about the internal secretions is that they are correlated with one another. Not only has this been abundantly demonstrated by experiment, but, in many cases, pathological lesions of the individual glands cause some disturbance in the functional relations of the other glands—the so-called "pluriglandular syndromes." The idea of a correlative status is not necessarily new, was perhaps implicit even in Bordeu's statement of the theory, but it did not begin to acquire tangible and intelligible form until the complex chemistry of the metabolism of the

body had been better understood. On the physiological side, it has been noted, for instance, that excision of the pancreas produces glycosuria, even after thyroidectomy and parathyroidectomy, but not after excision of the adrenal bodies; that partial excision of the thyroid in bitches will produce a mild myxedema, if pregnancy supervenes, the symptoms disappearing after littering; that the thymus gland is often enlarged in exophthalmic goiter but will atrophy after thyroidectomy; that castration is followed by enlargement of the thymus, and, conversely, excision of the thymus produces swelling of the ovaries. On the pathological side, the thyroid is often enlarged during puberty, menstruation, excessive venery (*e. g.*, in prostitutes) and pregnancy; swelling of the ovary and menstrual disturbances often accompany goiter. Myxedema often comes on at the menopause or in connection with sterility. Acromegaly, as was shown by Edwin Klebs, is often accompanied by enlargement of the thymus. Enlargement of the pituitary often accompanies pregnancy or hibernation, yet castration causes enlargement of the pituitary in the young and acromegaly is often associated with loss of sexual power. The fact that many of these experimental results and pathological findings do not harmonize makes the problem one of extreme complexity. Furthermore, it is known that lesions of different ductless glands will produce isolated identical effects, which overlap each other in a group of symptoms, making the causal relation dubious when there is a "pluriglandular syndrome." Glycosuria (lowered tolerance for carbohydrates) may be produced by goiter, by injection of thyroid extract in acromegaly, or by injection of pituitary extract, by excision of the parathyroid body, by injection of adrenalin, by excision of the pancreas, or by a lesion of the islands of Langerhans in that organ. On the other hand, an increased tolerance for carbohydrates (obesity) occurs after destruction of the posterior lobe of the pituitary body, as well as in myxedema or after thyroidectomy; increased blood pressure follows upon injection of the pituitary, adrenal, placental, and kidney extracts; lactation is accelerated by injection of extracts of the thymus, pineal, and pituitary bodies and the corpus luteum (ovary); the pupil is dilated by extracts of the thymus, pituitary, pancreas, suprarenals, kidney, sexual glands, liver, and muscle. Effects of this kind are analogous to the mystifying "enharmonic cross relations" in modern music, in which the same note (on the piano scale) is so employed that it is brought into relation with two different tonalities. C sharp and D flat, G sharp and A flat produce the same sounds when given on the piano scale, although they can, if necessary, be distinguished on stringed instruments, which render an exact account of the difference in the number of vibrations. Similarly, these apparently identical effects of the different ductless glands indicate that their functions are correlated, that they are somehow concerned in maintaining the hormonic equilibrium of the body.

Concerning the mechanism of correlation, two prominent theories have

been advanced. The first is the doctrine of the hormones of Bayliss and Starling (*b*) (1902), in which the chemical regulation of the body is assumed to be effected by means of hormones, or chemical messengers, which pass from the various organs and ductless glands, *via* the blood-stream, to other parts of the body, producing biochemical effects upon irritable protoplasmic tissues. Hormones are of two classes, those which excite the functions of organs containing involuntary muscle, and those which regulate morphogenesis, the latter being known more specifically as hormazones (Gley). In the initial experiment of William M. Bayliss and Ernest Henry Starling (*a*), the secretion of pancreatic juice following upon introduction of acid into the duodenum was found to be, not a local reflex, as had hitherto been assumed, but due to the action of a hypothetical substance (secretin) discharged by the intestinal mucous membrane under the influence of the acid and carried to the pancreas by the blood channel. As Keith expresses it, this experiment demonstrated that there is a postal system in the body *via* the blood channels, in addition to the telegraphic system *via* the nerves. Adrenalin, iodothyrin, and pituitrin are the only hormones of the ductless glands which have been isolated to date.[6]

The other theory is that of the clinicians and pharmacologists of the Vienna school, Hans Eppinger, Wilhelm Falta, and Nicolaus Rüdinger, which asserts that the suprarenal and thyroid bodies act upon and are controlled by the nerves of the sympathetic system, while the pancreas is similarly related to all nerves acting upon smooth (involuntary) muscle and not originating from the chain of sympathetic ganglia. The two systems of nerves have been termed "autonomic" by Langley, because they seem to be detached from and independent of the controlling impulses arising from the cerebrospinal axis, while themselves controlling all organs containing unstriped muscle, secreting glands, or both, e. g., the smooth muscle of the bronchi, stomach, intestines, blood vessels, genitalia, eye, and all the glands of external and internal secretion. The sympathetic or visceral nervous system has also been called the "vegetative" system, because the organs under its dominion functionate involuntarily or unconsciously, as with vegetables or plants. While some authors have limited the term "vegetative system" (autonomic system of Langley) to the thoraco-lumbar autonomic, which originates from the sympathetic ganglia, others include under this designation the whole visceral nervous system, i. e.; both the cervico-thoraco-lumbar autonomic (sympathetic system) and the antagonistic system governing involuntary muscle, which is largely made up of fibers from the vagus nerve and is now styled the cranio-sacral or "vagal autonomic." [7]

[6] That iodothyrin and pituitrin are actual hormones is doubtful, though each may contain hormones. Kendell's thyroxin is rather more probably a pure hormone than either of these.—R. G. H.

[7] Langley's own division of the entire autonomic system into sympathetic and parasympathetic components has much to commend it.—R. G. H.

The difference between the two autonomic nervous systems and the central (cerebrospinal) system is that, in the former, the nerve fibers never proceed, as ordinarily, directly from the nerve center to the organ controlled, but pass, as neurons, from the gray substance to a ganglion, in which they encounter a break or synapse (separating surface), on the other side of which a similar post-ganglionic neuron proceeds to the organ controlled. The synapse, a term first proposed by Sir Michael Foster, has been likened to a switch, over which the nervous impulse jumps to proceed on its way. J. N. Langley, the original investigator of the autonomic systems, discovered that wherever there is a switching of the nervous impulse across a synapse, the effect can be abolished, in other words the post-ganglionic fiber can be paralyzed, by painting over the exposed ganglion with nicotin solution, thus determining whether or not an autonomic nerve fiber passes through a ganglion without interruption. If, after painting the exposed ganglion with diluted 0.5 nicotin solution, or even after internal administration of the alkaloid, the effect of central excitation of the post-ganglionic fiber at the ganglion is the same as ordinarily, then there is no interruption; but, if the effect is abolished under these conditions, then the preganglionic fiber terminates in a synapse. Langley's nicotin effect holds good for all ganglia of the autonomic systems, whether of sympathetic or vagal origin. In other respects, however, these two systems are antagonistic, both in respect of physiological functions and response to the action of drugs. The effect of electrical stimulation of a sympathetic fiber is just the opposite of that of a vagal autonomic fiber. The sympathetic fibers check, the vagal autonomic fibers excite, the movements of the intestines; the sympathetic fiber dilates, the vagal autonomic contracts, the pupil; the sympathetic hastens, the vagal autonomic slows, the heart. Epinephrin, which the Viennese clinicians assume to be the specific hormone of the sympathetic autonomic, produces, on ingestion or injection,

Fig. 14.—John Newport Langley

effects similar to those produced by electrical stimulation of the sympathetic, viz., dilatation of the pupil, dry mouth from diminished salivary secretion, rapid heart action, glycosuria, and increased secretion and motility of the stomach and intestines. Hence, adrenalin, and drugs, like ergotoxin, which resemble it in action, are variously termed sympathicotropic, sympathicotonic, or sympathicomimetic. On the other hand, certain drugs, such as pilocarpin, muscarin, physostigmin, cholin, and digitalis, which stimulate the autonomic fibers of the vagus, producing effects diametrically opposite (contraction of the pupils, profuse salivation, slow heart action, pollakiuria, etc.), are termed vagotropic, vagotonic, or vagomimetic, because their action simulates the vagal autonomic. Thus, the Viennese clinicians postulate two opposing diathetic conditions, sympathicotonus and vagotonus, the symptomatology of which can be thrown into relief by certain pharmacodynamic tests, which have been likened by Januschke to "tuning keys, by means of which we can operate upon the complicated stringed instruments of the body, and voluntarily make one string tighter to increase its vibration or another looser to dampen its function" (Barker). These opposing conditions were included by S. Solis Cohen under a single syndrome, vasomotor ataxia (1892). To complete the analogy of their tripod of ductless gland correlations, Eppinger and Hess assume that the pancreas, controlled by the vagal autonomics, secretes a hormone "autonomin," which is supposed to antagonize adrenalin, the hormone of the sympathetic system proper. So far, this is a very cogent and fascinating theory, but, as often happens, it does not work out according to specifications in all cases, and is strongly opposed by Gley.[8] The symptomatology in vagotonic and sympathicotonic patients, too complex to be considered here, is extremely variable and the reaction to drugs sometimes unreliable. Thus, Eppinger and Hess themselves found that pilocarpin and epinephrin sometimes produce strong reactions in the same patient. The interest of their theory for present purposes lies in its capacity for elucidating the action of the ductless glands and internal secretion, for behind the ductless glands and the hormones themselves there must be some controlling mechanism. It is assumed that when the vegetative and vagal autonomics are overexcited (sympathicotonia, vagotonia), these act upon the viscera and the ductless glands, the hormones or internal secretions of which in turn react with redoubled force *via* the blood channels upon the autonomic nerve centers, vegetative and vagal. The theory is that the hormones of the viscera and the internal secretions of the ductless glands appear to regulate the tonus of the nervous system, while the autonomic nerve fibers themselves regulate the action of the ductless glands, the viscera, blood vessels, and all organs containing involuntary muscle. The importance of the subject in relation to clinical medicine has been well emphasized by Professor L. F. Barker (*a*) (1913):—

[8] For a recent critique on this topic see Vincent (*b*), 1917.

"In how far those sudden and violent excitations of the autonomic nervous system which accompany strong emotions are due to the intervention of the glands of internal secretion, and in how far they depend upon direct neural conduction from the brain, we are as yet but ill informed. I need only remind you of the vasodilatation of the face in the blush of shame, of the stimulation of the lacrimal glands which yields the tears of sorrow, of the palpitation of the heart in joy, of the stimulation of the sudoriparous glands which precedes the sweat of anxiety, of the stimulation of the vasoconstrictors, the pupil dilators, and the pilomotors in the pallor, mydriasis, and goose skin of fright, to illustrate some of these violent automatic excitations. While we do not yet understand the exact mechanisms of association among the activities of the cerebrum, the endocrine glands, and the reciprocally antagonistic autonomic domains and their end organs, we can begin to see the paths which must be followed, in order that more exact knowledge may be gained.

"The balance maintained normally between the two antagonistic systems is one of the most interesting of physiological phenomena. Think, for example, of the rate of the heart beat—how constantly it is maintained at a given level in each individual when the body is at rest: the impulses arriving through the vagal system just balance those arriving through the sympathetic system, so as to maintain a rate of approximately seventy-two beats per minute. And a similar balance is maintained in other autonomic domains (*e. g.*, pupils, bronchial musculature, gastric glands, gastro-intestinal muscle, sweat glands, bladder muscle, etc.).

"This equilibrium is all the more remarkable when one considers how frequently it is temporarily upset in the exercise of physiological function. The play of the pupils with varying light, the watering of the mouth at the smell of savory food, the response of the heart to exercise and emotion, the flow of gastric juice on adequate stimulation, the opening of the bile duct at the call of the chyme, the transport of the colonic contents through one-third of the length of the colon by means of one vehement contraction every eight hours, the sudden relaxation of the sphincter and contraction of the detrusor of the bladder in micturition, the violence of contractions in the domain of the nervus pelvicus in parturition in the female and in ejaculation in the male, come to mind at once as examples of sudden physiological overthrow of balance."

Another set of correlations advanced by the Vienna school is connected with the causation of diabetes. Eppinger, Falta, and Rüdinger regard the thyroid, pituitary, and adrenals (chromaphil system) as the accelerators or mobilizers of glycosuria, in that all three increase exchange or metabolism of proteins, the adrenals mobilizing carbohydrates and the thyroid increasing fat absorption. The pancreas and the parathyroids, on the other hand, are held to be inhibitors of glycosuria, retarding protein metabolism and restricting the mobilization of carbohydrates. Diabetes following excision of the pancreas is held to be due to the mobilizing power of the adrenal hormone on the glycogen of the liver, the normal inhibitory action of the pancreatic hormone being removed, and is thus at once a positive adrenal diabetes and a negative pancreatic diabetes. This harmonizes with the glycosurias following injection of adrenalin or following increase of the adrenal function from stimulation of the sympathetic system. Hyperthyroidism (exophthalmic goiter) produces a tendency to glycosuria from relative pancreatic insufficiency and increased adrenal activity. Myxedema or the corresponding removal of the thyroid gland produces an increased tolerance for carbohydrates (obesity), because the inhibitory function on the pancreas is removed and adrenal action diminished. There is a lowering of carbohydrate tolerance after parathyroidectomy. The lowered carbohydrate tolerance in hyperpituitarism and the increased tolerance in hypopituitarism, demonstrated by Cushing, is ex-

plained by the inhibitory action of the secretion of the posterior lobe of the pituitary on the pancreatic hormone, mobilization of glycogen and glycosuria resulting when the pituitary secretion is in excess and the restraining influence of the pancreas thus impaired. Cushing and Jacobson found that the obesity or high sugar tolerance following excision of the posterior lobe of the pituitary will persist even after subsequent excision of the pancreas, no glycosuria developing.[9]

The question arises, How do the internal secretions or hormones act upon the central nervous system? Here we encounter what Ehrlich calls "that obscure province of physiology," the specific irritability of organized tissues, or the capacity of protoplasm to react to chemical and other stimuli. If a chemical substance in the blood comes in contact with the chemoreceptors or special groups of atoms in the periphery of a cell, the two sets of substances may remain inert in relation to each other, they may combine, producing equilibrium, or they may induce a vigorous reaction through difference in their chemical potentialities. The complexity of this phase of the subject is fairly indicated in Abderhalden's studies of intracellular metabolism, in which he shows that by linkage of three different amino acids, *A, B, C,* the following isomeric arrangements can be produced by permutation and combination, viz.,

A-B-C *A-C-B* *B-A-C* *B-C-A* *C-A-B* *C-B-A*

In like manner, from linkage of four amino acids, 24 structurally isomeric compounds may result; from five, 120; from six, 720; from seven, 5,040; from fifteen, 1,307,674,368,000; from twenty, 2,432,902,008,176,640,000. We have as yet no calculus of variations fine enough to estimate even the rate of change of these evanescent combinations, which, we may assume, are constantly taking place within the cell.

Again, it may be asked, Is the hormonic equilibrium of the body identical with thermodynamic equilibrium? And here we have another problem which may be described as transcendental. In the ordinary metabolism of the body it is agreed that the first law of thermodynamics—conservation of energy or constancy of the sum of energy in an isolated system—applies in every respect. Does the second law—irreversible dissipation of energy in one direction—apply to such relatively isolated (adiabatic) systems as a cell enclosed in its cell wall or the animal body encased in its integument? Does the cell or the organism act like a heat engine or an electric cell, dissipating its energy in one direction, or is it a reversible mechanism, like a dynamo? In the animal body the foodstuffs of high chemical potential, proteids, carbohydrates, and fats, are degraded and

[9] The significance of all these phenomena is that of *bouleversement* or the enharmonic effect of dysfunction of a given gland upon other glands. A. J. Carlson (*c*) maintains that "there is absolutely no evidence, biological or clinical, of any one of the endocrine organs being able to function for the other. The beautiful diagrams and interrelations given me by Falta and his school are largely imaginary."

transformed into substances of low chemical potential (carbon dioxid, urea, and water), the energies passing, as in a Carnot cycle, from a source at high potential to a sink at low potential energy. The second law is operative here, but the process is more economical than in a heat engine. Still more economical is it in cold-blooded animals, while in green plants there seems to be an actual reversal of the process, in that substances of low chemical potential (nitrogen compounds, carbon dioxid, and water) are transformed into substances of such high chemical potentiality as carbohydrates, proteins, and oils. There is thus some indication that in plant cells, or those organisms, like bacteria, which lie between animals and plants, there is a possibility of reversal of those physical processes which take place in inanimate nature. Of this we have further examples in the nitrification of the soils by bacteria buried in it (without the aid of radiant energy from the sun) or in the Brownian movements of bacteria contained in a liquid (Johnstone). Of the possibility of reversing the second law in the human organism, Lord Kelvin said that, "even to think of it, we must imagine men with conscious knowledge of the future, but no memory of the past, growing backwards and becoming again unborn, and plants growing downwards into the seeds from which they sprang." This would assuredly be an extreme case, but Cushing's production of sexual infantilism in dogs by partial excision of the anterior lobe of the pituitary body fulfills some of these conditions. At best, we can only affirm that the whole matter is transcendental, that is, so far, beyond our ken, since it involves an assumption of the old metaphysical "vital principle," the *élan vital* of Bergson.

V

Of the internal secretions of the pancreas and the sexual glands, the thyroid, parathyroid, suprarenal and pituitary bodies, considerable is known; less of the spleen, carotid gland, and pineal body (epiphysis cerebri); of the "parathymoid" and the paraphysis of the brain, nothing whatever. Some of the most interesting phases of the subject, such as the relation of internal secretions to insanity, or the treatment of diabetes insipidus with pituitary extract by Barker and others, have only just had their beginnings. The vast amount of recent investigation on the subject has been well summed up in a number of excellent treatises. The earliest of these was that of Charles E. de M. Sajous (1903), which is, in effect, a complete system of medicine based upon the ductless glands. Sajous assumes that suprarenal, pituitary, and thyroid glands constitute the immunizing mechanism of the body, whence its germicidal and antitoxic substances are derived. Hence, the only use of drugs is to stimulate the internal secretions. Of more recent date are the treatises of Arthur Biedl (1910), Swale Vincent (1912), Wilhelm Falta (1913), Nicola Pende (1916), and Sir E. S. Schäfer (1916). Admirable surgical monographs

are those of von Eiselsberg on the thyroid gland (1901), Harvey Cushing on the pituitary body (1912), and W. S. Halsted on the operation for goiter (1919). In 1917, an Association for the Study of the Internal Secretions was founded in the United States, its literary organ or bulletin being *Endocrinology* (1917). In 1917, a special symposium on the relation of the glands of internal secretion to gynecology and obstetrics was held, by leading authorities, at the annual meeting of the American Gynecological Society.

The very complexity of the great mass of existing knowledge of the internal secretions indicates that it is in a state of flux. No attempt at a larger correlation or synthesis, which shall weld so many contradictory facts and opinions into a harmonious whole, has been successful to date. Only the surface of the subject has been scratched. Experimental evidence exists, equally in support of the doctrine of the Viennese clinicians that diathesis, or susceptibility to disease, is associated with the internal secretions, or of the doctrine of Sajous that they play an important part in the protective mechanism of the body. Again, it seems plain that no single ductless gland can entirely replace another gland as to function, and that seemingly identical effects or overlapping of functions of different glands are, like the auditory effects of enharmonics in music, illusory. The effect of different glands upon mobilization of glycogen, or of tumors of the adrenal, pituitary, or pineal upon genital conformation are really compensatory effects, over- or underactivity of the pancreas or the sexual gonads to set off the opposite condition elsewhere. Finally, the embryology and histology of the ductless glands reveal complexity rather than simplicity of structure, so that the best guide in their investigation has been Sir Michael Foster's dictum that no important organ in the body has a solitary, exclusive physiological function.

Organotherapy and Hormonotherapy . . . . *John T. Halsey*

Introductory—The Thyroid—Pharmacology—Therapeutic Employment—Myxedema and Cretinism—Hypothyroidism—Goiter—Exophthalmic Goiter—Obesity—Empiric and Symptomatic Thyroid Therapy—The Parathyroid Glands—Tetany—Parathyroid Insufficiency—Paralysis Agitans—Other Convulsive Conditions—The Hypophysis Cerebri—Hypophyseal Hormonotherapy—The Anterior Portion of the Pituitary Gland—Organotherapy with the Whole Pituitary—The Corpus Pineale—The Suprarenals—Pharmacodynamic Actions of Epinephrin—Organotherapy with Suprarenal Substances—Symptomatic Suprarenal Therapy—Empiric Suprarenal Therapy—The Thymus—Testicle—Ovarian Substances—Placenta—Mammary Gland—Pancreas.

Organotherapy and Hormonotherapy

JOHN T. HALSEY

NEW ORLEANS

Introductory

While in ancient writings there are numerous references to the administration, for medical purposes, of various preparations of animal origin, it is evident that for the most part this use was the result solely of religious conceptions and was entirely void of any rational basis. To a relatively slight extent, however, such substances were used by the ancients in what may, considering their almost complete ignorance of physiology and pathology, be considered a rational fashion, as in the administration of cow's udder as a lactagog, of the genitalia, including the testicles, to increase sexual power, and of various organs in the treatment of disease of the same organs, a type of therapy revived in the 16th century by Paracelsus and others, of which we still see traces even at the present time.

The only connecting links between the organotherapy of those days and that of to-day is to be found in the administration of testicular and mammary products as aphrodisiac and lactagog, respectively.

Although the greater portion of Brown-Séquard's (*b*) claims have not, up to the present time, been confirmed, modern organotherapy dates from his report in 1889 of the effects which he had experienced in his own person as a result of taking injections of a testicular extract. Its first real triumph, however, was obtained when Murray in 1891 administered thyroid extract in his historical case of myxedema. In the less than thirty years which have passed since this epoch-making discovery, the study of the therapeutic effects of this and other endocrin products has been industriously pursued, until to-day their use in the treatment of disease has become one of the most important and useful phases of therapeutics.

At first it was believed that such glandular preparations could act only substitutionally, that is, that the substances administered acted in place of the absent or diminished secretion of the patient's gland, but very soon it became apparent that all the results obtained could not be explained so simply, and that there must be other modes of action.

Later the demonstration that these glands contained substances possessing a wide variety of pharmacodynamic powers, and that some of these

substances could influence the function of one or more of the other endocrin organs, widened our conception of the fashion in which these substances produce their effects.

Not so very long ago it seemed well to classify the therapeutic employment of the endocrin gland preparations under the two headings of organotherapy and hormonotherapy. By organotherapy was meant their employment in conditions in which the effects appeared to be due to a replacement of or making good of a deficiency of the internal secretion of the patient's own endocrin organ or organs, while the term hormonotherapy was used to include their use in conditions in which they appeared to act by virtue of their possession of pharmacodynamic powers strictly comparable to those possessed by ordinary drugs. In this article the term organotherapy will be used to include all the uses of endocrin preparations except such as appear to rest purely on empiricism and those which appear to be based on their pharmacodynamic powers.

Borchardt (*c*) has recently attempted to define and give a name to the various fashions in which endocrin products produce their therapeutic effects. While the attempt does not appear to have been altogether successful his discussion is interesting and helpful, and for that reason is reproduced here in very much abbreviated form. This writer defines and classifies the various types of organotherapy and hormonotherapy as follows: 1. Substitutional hormonotherapy, the administration of endocrin preparations to overcome the effects of a deficiency or disturbance of the function of this same gland, as, for example, the administration of thyroid substance in a case of myxedema. 2. Vicarious (durch Wechselwirkung) hormonotherapy, in which the administration of a preparation of one gland compensates for, or overcomes the effects of, dysfunction of another endocrin organ. Examples of this type of therapy are the thymus treatment of exophthalmic goiter, and the thyroid treatment of tetany. 3. Hormonal immunotherapy, such as the use of Moebius' serum in Graves' disease. 4. Hormonal ferment therapy where the glandular product acts by virtue of its ferment content, as in the use of pancreas preparations for their action in the alimentary canal. 5. Pharmacodynamic hormonotherapy, in which the effects produced are the results of the exertion of pharmacodynamic powers possessed by the endocrin preparation. The treatment of asthma by suprarenal substance and the induction of labor by the administration of pituitrin are instances of this type of therapy. Borchardt * believes that endocrin substances may exert a therapeutic action in still a sixth fashion, namely, by activating the protoplasm so as to increase its ability to form antibodies, an effect comparable to that resulting from the injection of foreign protein and speaks of this as hormonal therapy through augmentation of function (leistung-steigernde Ther-

* See Addendum, p. 150.

apie). It would seem that to these six types of Borchardt's, a seventh might well be added, which may be called reciprocal hormonotherapy, by which is meant the administration of one gland for the purpose of influencing the function of another, as when thyroid is administered in the attempt to so influence the ovarian function that this in turn will correct menstrual disorders.

Any one familiar with the literature dealing with the employment of endocrin preparations must be struck by the very unsatisfactory character of a large proportion of the reports that have been published. In many of those emanating from the laboratory and in a still larger proportion of clinical reports, there is such an absence of sufficient detail that the reader, if he be at all critically minded, is left entirely uncertain whether the conclusions reached and the claims made are in any degree in accordance with the facts. As a result of its relative newness and of its complexity (conditions but partly understood being treated by agents whose powers are even less comprehended), the present status of endocrin therapy is very uncertain. One seeking to analyze and correctly evaluate the claims made as to the therapeutic efficiency of these various substances is confronted with a task of such complexity that he must expect often to fail, accepting at times that which is false and at others rejecting the true. No one can be more convinced of his liability to error than one who has just completed his attempt to perform this task.

The writer of this portion of this work, in his discussion of various phases of glandular therapy, has endeavored, whenever he was able to form a definite opinion, to express himself either definitely for or against the clinical value of various uses of these products, or to express the varying degree of faith therein that the available data may justify. It has been his aim whenever, in his opinion, the evidence indicates that there is even a probable relationship between the results claimed and the treatment applied, to present the evidence and express his own estimate (or that of others) of its clinical significance. In some instances certain applications of endocrin therapy have been discussed, not because they have appeared to him to be of real value, but because in endocrin literature, especially that issued as propaganda, claims are made for their efficiency that are not in accord either with known facts or reasonable conjecture.

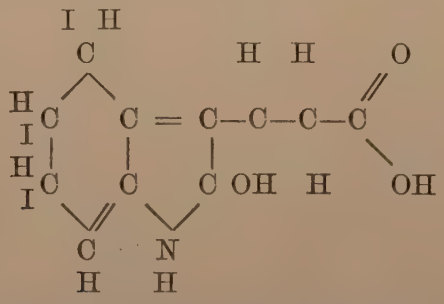
Nothing seems to have been more clearly established by his search of the literature than that there is urgent need of more careful observation and more correct reporting of the results or lack of results of glandular therapy. Fortunately there are many indications that the time is already at hand when the clinical observations of this type of therapy will be conducted and reported with the same accuracy as are those of the laboratory.

The Thyroid

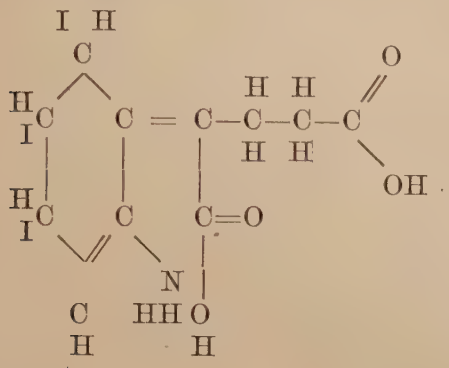
Among all the endocrin products used in therapeutics, no other has up to the present time been used with such brilliant results or found so wide a field of usefulness as have those made from the thyroid gland. Although Brown-Séquard's employment of testicular extract has the distinction of being the first rational attempt to utilize a product of this type as a therapeutic agent, it was Murray's discovery that thyroid administration produces such remarkably beneficial effects in myxedema that first demonstrated beyond all doubt the therapeutic value of preparations made from an organ of internal secretion. Notwithstanding that ignorance and credulity have led many physicians and surgeons to make exaggerated and unfounded claims for their therapeutic value, the experience of the three decades that have elapsed since Murray's first report has firmly established thyroid substance as one of the few absolutely indispensable drugs of our pharmacopeia, with an already wide field of proven usefulness, which in the future may be greatly increased.

Pharmacology

Chemistry.—The real beginning of our knowledge of the chemistry of the thyroid was Baumann's discovery in 1895 that it contained iodin in organic combination, and the demonstration by him and others that the specific action of the gland and its therapeutic actions were dependent on and exerted only by this iodin containing substance or substances, generally believed to be of proteid nature, until Kendall (*e*) in 1915 isolated from the thyroid a crystalline substance containing 60 per cent of iodin. This substance named by him thyro-oxy-indol (to emphasize the presence in it of the oxy-indol nucleus), which is shortened for convenience to thyroxin, has been analyzed and synthetically prepared (Kendall (*g*) (*h*), 1918) and shown to possess the structural formula:



Further investigations have led Kendall to the opinion that in the body this structure exists in a different form (the indol ring having opened) with the formula:



It would appear that this substance exerts many if not all of the therapeutic actions of thyroid extracts, both laboratory investigations and clinical trials conducted in the Mayo clinic having demonstrated that it can entirely replace thyroid extract in the treatment of myxedema (Kendall (*f*) (*g*), 1917, 1918).[1] Thyroxin is very insoluble in alcohol, ether, water, acids, and sodium carbonate, but readily soluble in dilute alkali and ammonia.

Several authors have claimed the successful isolation in more or less pure form of the active principle or principles of the thyroid, among others, Oswald, who believed that the therapeutic activity was exerted mainly or entirely by a globulin named by him thyroglobin. Beebe's views as to the significance of different substances isolated by him have not been generally accepted.

Although Kendall's discovery of thyroxin is of great interest and doubtless also will prove of clinical value in the future, for the present more practical importance attaches to the fact that the physiological activity (and therefore the therapeutic efficiency) of thyroid preparations appears to run parallel to their iodin content, and that this varies within very wide limits, Hunt and Seidell finding, in preparations on the American market, a variation of 400 per cent (0.095 to 0.38 per cent). Whatever the true nature of the active principle or principles may be they are relatively stable substances, and resistant to heat so that they may be readily sterilized.

Absorption and Fate.—The active substance or substances are readily absorbed from the alimentary canal and when thus administered produce their characteristic effects. Kendall (*i*) (1919) found that of 200 mg. of thyroxin injected intravenously, 43 per cent was excreted in the bile and 13 per cent in the urine during the next fifty hours. The rest, he believes, was removed from the blood stream by the thyroid gland.

[1] Kendall (*f*) (1917) considers it by no means impossible that the thyroid contains at least one other active principle, as in the Mayo clinic it has been found that some of the symptoms of myxedema were relieved by certain thyroxin-free fractions of thyroid extract, which were obtained while isolating thyroxin.

Plummer (personal communication quoted by Kendall, 1918) has shown that in man the maximum effects of a single intravenous dose of thyroxin are reached only after ten days, and that the effects persist for eight or ten days longer.

Pharmacodynamic Actions.—Oral and intravenous administration of thyroid extracts (Fawcett, Rogers, Rahe, and Beebe) or of thyroxin (Kendall (*a*), 1914) are followed by no immediate pharmacodynamic effects on the blood pressure or heart rate. It is only 24 to 36 hours later that the heart rate rises decidedly, this effect being accompanied by restlessness and a slight temperature elevation. The effects ordinarily obtained after a time from administration to normal animals of sufficient amounts of thyroid substance are a striking increase in the rate of metabolism, accompanied by a rise in temperature, diarrhea, loss of weight, tachycardia and nervousness. In man, thyroid feeding produces similar effects so that a symptom complex may develop which in many particulars resembles that of Graves' disease, while in individuals already suffering from this disease thyroid administration almost invariably aggravates the condition. In thyroidectomized animals its administration is able to completely overcome (for the time) the effects of the removal of the gland, and comparable results can be produced in cretins and myxedematous patients.

The effect on the metabolism, which is one of the most striking and constant of the effects produced by feeding, has been most extensively studied. Almost without exception, these studies have shown that, no matter how administered, thyroid substance invariably brings about an increase in the total metabolism (proteid, fat, and carbohydrates). There is often an especially marked effect on proteid metabolism leading as a rule to a negative nitrogen balance.[2] While, particularly with large doses, the combustion of proteid is especially augmented, a negative nitrogen balance may be avoided by a diet containing a sufficiently large number of calories, an extra quantity of carbohydrates being especially efficacious in this respect. The effects on metabolism manifest themselves most strikingly in thyroidectomized animals and in human cases of hypothyroidism.

Normal individuals show a very remarkable difference in their susceptibility to this drug, a fact which is of considerable clinical significance and for which no entirely satisfactory explanation can be given. Small doses frequently repeated are much more toxic than an equal or larger amount administered at one time.

[2] Janney found that an increased nitrogen retention followed the administration of very small doses in cretins and in one case of exophthalmic goiter, although in normal individuals similar doses caused lessened nitrogen retention. In rats Hewitt also found that very small doses of thyroid caused an increased nitrogen retention and gain in weight, which may have been due to increased appetite and greater consumption of food.

Therapeutic Employment of Thyroid Preparations

Thyroid therapy produces its most remarkable and valuable therapeutic effects in myxedema and cretinism, that is, in conditions clearly due to absence or deficiency of the thyroid function. It has also been employed in the treatment of a large number of diseases or conditions, in some of which there is more or less reason for believing that hypofunction or dysfunction of the thyroid plays a causal rôle. In other conditions in which it is claimed that this therapy is of benefit, there are not sufficient grounds for the assumption of faulty thyroid function, and the justification for its employment must be sought in assuming that it acts symptomatically.

Myxedema and Cretinism.—Organotherapy obtained its first and, up to the present date, its greatest triumph when in 1891 Murray, inspired by Bettencourt and Serrano's fairly satisfactory results from transplantation of a sheep's thyroid in a case of myxedema, undertook to treat a case of myxedema by the subcutaneous injection of a thyroid extract. The brilliant success of thyroid therapy in this historical case is known to all and is manifest in the fact that by thyroid administration this woman, a pronounced case of myxedema of twelve years' standing, was promptly restored to and maintained in good health for nearly thirty years, up to the time of her death a few months ago. Very soon it was found by Hector Mackenzie and by Horwitz that the oral administration was just as efficient as, and far less inconvenient than, the injections. Physicians everywhere adopted the treatment and quickly obtained similar brilliant cures in myxedema, both the spontaneous form and that occurring after removal of the gland (cachexia strumipriva), and a little later, in cases of cretinism. To-day the value of this treatment is universally recognized and the method of its application is well known.

The remarkable change wrought by it in the condition of the patients must be seen to be believed. In cases of myxedema the usual result is a complete cure with disappearance of all the symptoms. The results have been well described by v. Jauregg: "One of the first signs of improvement is the rise to a normal level of the formerly subnormal temperature which leads to the disappearance of the great sensitiveness to cold. Coincidentally the pulse becomes more frequent. In a few days the effect on the skin is manifest, the edema and thickening diminishing and eventually completely disappearing so that the skin becomes soft and smooth, and is no longer abnormally dry as the sweat glands resume their function. The hair grows better, that on the head becomes longer and thicker and is no longer dry and brittle. Often the hair returns even on entirely bald spots, and the scanty or absent eyebrows are renewed. As a result of the changes

in the skin and subcutaneous tissues, the face and hands regain their natural appearance and the stiffness in the limbs disappears. There is a loss of weight which may amount to as much as forty pounds or even more. The feelings of weakness and fatigue, so characteristic of these patients, are replaced by consciousness of increased energy and desire for activity, the movements of the patient becoming quicker and more dextrous. The mental condition also improves rapidly, memory returning, and understanding and will power increasing. The sleepiness or stolidity is succeeded by a more normal state of mind, the patient becoming more talkative and beginning to take a normal interest in his environment so that he is no longer moody and depressed." Even when there has been a real mental disturbance, this is usually completely cured, although in some cases there may be complete restoration of the general health without cure of the mental disturbance. The appetite and digestion improve, constipation is relieved, and diuresis increases. The more or less atrophied genitalia return to a normal state in patients sufficiently mature, and menstruation and other genital functions are restored.

In *cretins* thyroid therapy also produces most remarkable results, the most constant of which is the effect on growth. Under the influence of thyroid feeding this is markedly stimulated even in subjects who for years had not increased in stature and who had arrived at an age in which, in normal individuals, growth has ceased.

In forty-nine out of fifty-one cretins to whom thyroid was administered for from three to six years, von Jauregg obtained an increase of stature, which exceeded the normal average for the corresponding age and intervals; and others have published large series with similar results. Most of the following figures are quoted from v. Jauregg; increased growth in fifty-two of fifty-nine cases treated for from one to three years (v. Eysselt); in 85.7 per cent of 440 cases under treatment for from one to one and one-half years (Kutschera von Aichberger), among which were two subjects aged 25 and 26 years, who grew 3 cm. and 7.5 cm.; in twenty-three of his own series of fifty-one cases von Jauregg obtained a growth ranging from 10 to 15.5 cm. during one year of treatment, one subject, 27 years old, growing 4 cm., another, 23 years old, 12.5 cm., while a third, a girl of nineteen, increased her height from 107 to 135 cm., and a fourth under treatment from his fifteenth to his twenty-second year, increased his stature from 105 to 160 cm. (from 42 to 64 inches). Of v. Eyselt's cases, four subjects, aged from 20 to 23 years, grew from 6.5 to 22.5 cm. and Christoffersen's patient of 45 years grew 5 cm.

The rate of growth is greatest during the first year of treatment, after that gradually approaching the normal. In v. Jauregg's own series the average growth in successive years of treatment was 9.5, 6.3, 5.5 and 5.7 centimeters.

If treatment is started early enough normal stature may be attained,

but where medication has been delayed such results cannot be expected. Not infrequently the very rapid growth resulting from thyroid treatment is attended by the undesirable result that the rapidly growing bones are too soft, bowlegs or deformity of the spine resulting. The delay in dentition, so regular a feature of cretinism, is also corrected. Even patients of relatively mature age may develop new teeth, Sinkler having seen this in a patient of thirty. The abnormal conditions of the skin, hair and nails, the tendency to obesity, the pseudolipomata, the swollen tongue, the goiter, the hypoplasia of the genitals and other physical features of cretinism also yield more or less completely and promptly to the treatment, and coincidently with these physical results there is an improvement or return to normal of various functions, the metabolism becoming normal, the appetite and digestion being improved, and the constipation (almost regularly present in cretins) corrected, while in patients sufficiently mature the genitalia develop, menstruation is established and the other sexual functions become more normal. Such effects on the development of the genitalia and on their functions may be obtained even at a relatively advanced age, as in Murray's patient, aged 27 years. Improvement in the hearing may or may not be obtained, depending on the cause of its impairment, but in a very large percentage of cases this function is also favorably influenced.

While thyroid feeding almost invariably brings about at least some improvement of the mental condition of the cretin, there are great differences in the results obtained. Promptness in inaugurating treatment is of preëminent importance for securing the best results. Cases in which there is only a delayed mental development, especially if they are treated early, usually respond with a prompt and marked improvement, so that after a time their mental and psychic status approximates if it does not equal that of normal children. Unfortunately, even in the apparently milder cases such gratifying results are not always attainable, for not infrequently the improvement in the physical status far exceeds that in the mental. Although, as has been intimated, complete return to a normal mental state does not always ensue even in the milder cases, the improvement is almost invariably so great that the lot of the patient is greatly ameliorated and his ability to care for himself markedly increased. In those cases in which there is a true weakmindedness or idiocy, as is often the case in congenital cretinism, one may not hope for more than an improvement in the mental condition sufficient to render the subjects less helpless and more amenable to control and care.

It is thought by many that in some cases at least of myxedema and cretinism the thyroid feeding brings about favorable changes in the condition of the more or less atrophied thyroid glands. Against the correctness of this view is the fact that practically always cases of true myxedema relapse if the treatment is abandoned. An argument for it is seen by some

in the fact that almost universally after thyroid has been taken for a time, the dose may be decreased to one-fifth or one-tenth (or an even smaller fraction) of the dose required at the commencement of the treatment. It is entirely possible, although not definitely proven, that the thyroid, which is administered, acts not only substitutionally (i. e., by supplying the deficiency of thyroid secretion), but that just as it acts beneficially on the function of various organs, it may also improve the function and perhaps, too, restore to a healthy state such thyroid tissue as may still be present and able to function.[3] It is also not impossible that the improvement in function of other endocrin glands, resulting from the thyroid administration, may in turn exert a favorable influence on the diseased thyroid.

Dosage.—In all these conditions, whether classed as myxedema, cachexia strumipriva, or cretinism, the indications for and details of the administration of thyroid are essentially the same. With the varying degree of deficiency of function, however, there are marked differences in the doses necessary and in the results obtained. The correct dosage can be determined only by trial and varies within wide limits.[4] It is well to start with relatively small doses which will be increased or diminished according to the effects obtained. While in many cases doses ranging from 1 to 5 grains of the dried gland per diem will be found sufficient, occasionally, at the commencement of the treatment, much larger doses, up to 15 or 20 grains (or very rarely even more) may be necessary, but such doses are dangerous. Once the desired effect has been obtained, it is the almost universal experience that it can be maintained by much smaller doses. In an adult case of ordinary severity, a daily dose of 3 to 6 grains of the dried thyroid will usually suffice in the early stages of treatment, and 1 to 2 grains daily will usually be sufficient as a maintaining dose.[5]

In cretins the dosage is (in proportion to the weight) the same as in myxedema but occasionally much larger amounts are required. Sajous (1919) gives the following as average dosage: For an infant, ½ grain daily; at two years, ½ grain twice daily; older children, 1½ to 2 grains daily. Von Jauregg believes that the failures of treatment reported by certain authors were due to too large doses. He has found it best to start with 0.1 gram (1½ grains) per diem and to increase this only gradually. An initial dosage of 5 grains daily will, he states, at least

[3] That thyroid administration can exert an influence on the thyroid gland tissues is shown by the results of thyroid therapy in goiter. That it can strikingly stimulate thyroid function seems proven by the disastrous results which have followed thyroid feeding in some cases of exophthalmic goiter.

[4] Plummer has shown, however, that the determination of the basal metabolic rate will enable one to calculate the necessary dose of thyroxin very closely.

[5] Cases have been reported in which very much smaller doses sufficed to maintain a satisfactory condition, Murray having reported one case in which a small dose every two weeks was sufficient, while Zum Busch reported two cases in which 5 grains every two weeks kept the patients in a satisfactory condition. (Quoted from von Jauregg.)

occasionally cause serious results. It is undoubtedly safest and best to start with small doses, which can be increased if necessary.

As a general rule there should be little difficulty in determining by trial and by observation of the mental and physical status of the case, the amount of the drug necessary at the different stages of the treatment. Determination of the effect produced on the basal metabolism is probably the most accurate means of determining the correct dose, but for obvious reasons this method will be available only occasionally. Signs of overdosage in myxedematous patients (and in cretins) are a rise of temperature above normal, too great acceleration of the pulse, too rapid and excessive loss of weight, headache, pains in the limbs, flushing of the face, feelings of weakness, profuse sweating, tremors, loss of appetite, vomiting, diarrhea, and, of more serious portent, attacks of palpitation of the heart, anginal attacks or cardiac failure. In not a few instances death from cardiac failure has occurred during treatment. Skin affections, such as urticaria and furunculosis, have also been attributed to the thyroid medication. In view of the occasional occurrence of such disagreeable and, more rarely, of really serious effects, these cases must be kept under close observation in the first months of treatment and under no circumstances should a patient be allowed to take any but small doses unless frequently seen by his physician. Especial caution must be exercised in the treatment of more advanced cases, for whom the initial dosage should be small, and it is best that such patients should be confined to bed, or at least to one room, until the correct dosage has been determined and until there is a decided improvement in health and strength.

In cases both of myxedema and of cretinism attempts have been made to overcome the thyroid deficiency by *implantation of thyroid* tissue, one of the first of these (that of Bettencourt and Serrano) having been the inspiration for Murray's institution of thyroid therapy in his historical case. While often the grafts take and for a longer or shorter period cause and maintain a more or less satisfactory improvement quite comparable to that obtained by thyroid feeding, experience has shown that after a time the grafted tissue is absorbed or loses its specific powers so that the patient suffers a relapse. Kocher (*a*), in 1914, concluded that experience has shown that, while grafting gives prompter and better results than thyroid feeding in myxedema, it is not possible to obtain permanent results from one grafting.

The first of these transplantations was performed by H. Bircher in 1889, and following the report of his two cases thus treated with temporarily beneficial results, transplantation has been fairly frequently performed by other surgeons with similarly temporary results. In 1907, Christiani reported 28 cases of myxedema (spontaneous and post-operative), cretinism, faulty development, dwarfism, and infantile obesity, in which he implanted thyroid tissue with very great improvement in 60 per

cent, remarkable results in 34 per cent, and no distinct improvement in 6 per cent. He gives no details, but claims that there were often permanent results (results definitifs). As recently as 1916 Kummer (quoted by Sajous) has reported a successful autograft.

In view of the superiority of the results obtained by thyroid feeding, the reported results of implantation do not justify its performance.

Hypothyroidism (Myxoedème fruste)

Unquestionably there are numerous individuals in whom the function of the thyroid glands is permanently or temporarily more or less deficient and in whom such deficiency is a cause of various disturbances of health and function. The frequent occurrence and the clinical importance of the recognition of these cases of slight hypothyroidism has been especially emphasized, first by Hertoghe (*a*) (*b*) (*c*) and subsequently by many others, notably by Leopold-Levi and Rothschild. There can be no question that many of those who have maintained that hypothyroidism is the cause of manifold and various disturbances of health and function and who have reported remarkable results from thyroid therapy in a long list of diseases and symptoms, have been carried away by their enthusiasm and have seen in disturbed thyroid function the cause of, and have found in thyroid therapy a cure for, diseases and symptoms neither due to faulty function of the thyroid nor curable by its administration. On the other hand, there can be as little question that there is much that is true in many of the claims made by adherents of these views. It is in the analysis and correct evaluation of these claims, especially of those made for the therapeutic efficiency of thyroid feeding, that the student of organotherapy finds one of his hardest tasks, and his conclusions will vary, depending on whether he is an optimist or a pessimist in his attitude toward therapy. In general it may be stated that where the causal relationship between faulty thyroid function and disturbance of health has been definitely demonstrated, thyroid administration has proven its value, that in some other conditions, in which such proof is lacking, the results of thyroid therapy, which have been reported, are such as should convince all but the most skeptical of its real value, but that the evidence as to the value of thyroid administration in still others of these conditions is such that the claims made must be rejected entirely or received with more or less decided skepticism.

The salient points in these cases of moderate hypothyroidism are a subnormal temperature, a slow pulse, obesity, roughness and dryness of the skin and hair, constipation, disturbance of menstruation and of other genital functions, and also certain nervous and mental symptoms such as sluggishness, stolidity, and somnolence with lack of energy and abnormal fatiguability. There is also, as Leopold-Levi and Rothschild have em-

phasized, a group of patients with thyroid instability in which stages of hyperthyroidism and hypothyroidism alternate. These authors also believe that hypothyroidism is very often the sole or main cause of migraine, chronic arthritis, mucous enteritis, urticaria and other skin affections, especially acne and eczema, and of mental symptoms.

It cannot be questioned that, when any of the above mentioned disturbances are present in cases of hypothyroidism, thyroid administration often proves strikingly beneficial and it appears equally beyond question that the majority of the medical profession, as they do not realize the possible thyroid causation (partial or complete) of such conditions and symptoms, do not sufficiently often make use of thyroid feeding in their treatment. However, the fact that thyroid administration will relieve constipation, amenorrhea, migraine, arthritis, and so forth, in hypothyroid individuals is no proof that, as some enthusiasts believe, this treatment will be beneficial in all or even in the majority of patients suffering from these complaints. It would appear therefore that the therapeutic lesson to be drawn from the reported successful employment of the thyroid, in such conditions as have been enumerated above, is that the physician should bear in mind the possibility that they may be expressions of thyroid insufficiency and that therefore a cautious trial of thyroid therapy is not only justified but indicated, at least in subjects in whom careful observation indicates, with some degree of probability, that the thyroid may be hypoactive.

Dosage.—The doses required in these cases of mild or doubtful hypothyroidism are usually very small. For an adult the initial or tentative dose should be from 1/10 to ⅓ grain three times a day, and it should be increased only gradually if at all. It is especially important to give only small doses if there be any doubt as to the hypothyroidism. Larger doses than 1 or 2 grains three times a day will rarely if ever be required in this type of case, and the effects of even the small doses must be carefully noted if harmful or even disastrous results are to be avoided.

Goiter

Thyroid therapy exerts a so unmistakably favorable effect on goiters (other than those of hyperthyroidism) that it has been extensively used both for therapeutic purposes and, especially during an earlier period, as a method of testing the activity of different thyroid preparations.[6] To Reinhold belongs the credit of this discovery, which was promptly confirmed by others, notably by von Bruns. The demonstration that thyroid

[6] The actuality of this action has been most conclusively demonstrated not only by thousands of clinical observations but also in such experimental studies as those of Bruns who, by examination of segments of the goiter, removed before and after the administration of thyroid, was able to demonstrate histologically that tissue changes of a beneficial type had resulted.

therapy produces such results is of peculiar interest, and is of great significance for the theory of thyroid therapy in particular and of organotherapy in general, for it furnishes the proof that ingested thyroid substance can exert a curative influence on a diseased thyroid.

While this beneficial action on certain types of goiter has been clearly established, it remains doubtful whether thyroid medication is more effective than, or even as effective as, the administration of iodid. Clinical opinion on this question is divided. A. Kocher and many others consider it no more efficient than iodid, and others, probably the majority, believe it inferior, but v. Jauregg quotes several observers who have reported successful results from thyroid feeding in cases in which iodids had failed. A great objection to the thyroid therapy of goiter is that by no means rarely its employment has resulted in the development of a condition of hyperthyroidism. It would seem that at least occasionally a case of apparently simple goiter, exhibiting few or no signs of hyperthyroidism, is in reality a case of latent Graves' disease. In such a case the administration of thyroid is almost certain to prove harmful, perhaps disastrously so.[7] As a rule when thyroid substance is administered in these cases the effects are manifest in a few days and reach their maximum within two to four weeks. Usually the results are not permanent, a relapse occurring within a few months, if the medication be discontinued. If in three weeks no results are obtained the case is probably not amenable to thyroid treatment. Results are better in the goiters of children than in those of adults.

Dosage.—If used at all in the treatment of goiter, thyroid should be used cautiously. There is no justification for ever giving large doses, and it is best to start with a daily dose of not more than 1 to 1½ grains, which should not be increased until observation during at least a week has shown that there are no deleterious effects, and then only to a daily dosage not exceeding 5 grains. Satisfactory results have been obtained from the administration of various thyroid preparations such as iodothyrin, thyreoglobulin, and thyroxin. While it has been thought by some observers that one or another of these preparations proved more effective than dried thyroid, the direct converse has been claimed by others. Probably the effects of these preparations differ from each other only quantitatively, so that with proportionate dosage similar effects will be obtained with any good thyroid preparation.

Exophthalmic Goiter (Graves' Disease)

The weight of clinical opinion appears to be overwhelmingly against the use of thyroid therapy in exophthalmic goiter and in other conditions

[7] The same objection may be made, but perhaps with less force, against the use of iodids in the treatment of goiter.

of hyperthyroidism, on the grounds that it rarely if ever proves beneficial, and that, by no means rarely, its effects are most harmful. Moebius, at a time when this view was by no means general, insisted most strongly that in this disease thyroid should not be given; Biedl has expressed his belief that its administration to these cases is *always* followed by bad results, and A. Kocher says emphatically that "the avoidance of thyroid or iodin administration is the first and most important indication" in the treatment of Basedow's disease. Von Jauregg's opinion is that "as this disease is looked upon as a condition of hyperfunction of the thyroid, it is to be expected that thyroid therapy will act unfavorably and aggravate it," and that "this expectation has been fulfilled by the results of trial." The last named writer is also convinced that it is contraindicated, not only in well developed cases, but also in cases of latent Graves' disease. Bram, in his recent book on exophthalmic goiter, mentions this treatment only for the purpose of condemning it except in cases which show signs of hypothyroidism. If necessary, a much longer list of such condemnatory opinions could be compiled, but it is believed that these sufficiently represent the views held by the majority of those who have had a sufficiently large clinical experience.

While these views and others of like import are based in part on the assumption that thyroid administration must of necessity act harmfully on patients already suffering from the results of overactivity of this gland, it would appear that they have received ample confirmation in the following indisputable facts. It has been the experience of at least a large majority of competent clinicians, who have had the opportunity to observe the effects of thyroid administration to patients suffering with this disease, that these effects have rarely if ever been beneficial but have almost always been harmful and in some instances fatal.[8] In addition a number of cases have been reported in which thyroid medication was responsible for the development of Graves' disease.

On the other hand, at one time, not so long past, a considerable number of physicians was of the opinion that thyroid therapy was at least occasionally productive of distinctly beneficial results. Of late the adherents of this view appear to have become less numerous, for in the recent literature this treatment is advocated less frequently. Among those who still believe that there are cases of Graves' disease, which, under certain conditions, are benefited by small doses of thyroid, is Rogers of New York.[9] As a justification for belief in the efficiency of thyroid medication in cer-

[8] It is noteworthy that Forchheimer, who believed that a small percentage of these cases were benefited and some cured under thyroid or iodin treatment, stated that the only fatal result, which he had seen in an experience of over thirty years, was due to thyroid feeding.

[9] While I have not been able either to grant his premises or to follow his reasoning, the reports of the successful employment of thyroid medication, which have been made by Rogers are such that they cannot be rejected offhand. As, however, this section of this work deals only with the thyroid therapy of Graves' disease and Rogers'

tain cases of exophthalmic goiter, the hypothesis has been made that there are cases in which the overactivity of the gland has been caused as follows: Originally in these cases the thyroids are hypoactive and produce too small an amount of secretion. This deficit of thyroid hormone then reacts on other organs and tissues in such fashion that they are caused to call on the thyroid for increased activity, with the result that the fatigued or diseased thyroid responds to this stimulus by an overproduction of its hormone, which then causes the symptoms of hyperthyroidism, although the case is (according to this hypothesis) in reality a case of hypothyroidism. The hypothesis, while ingenious, appears not only to lack all basis of demonstrated fact but also to be so fantastic as to justify its prompt rejection.[9a]

After all, until we obtain a fuller understanding of Graves' disease, the question as to whether or not thyroid therapy is even occasionally useful in it must be settled by close clinical observation of cases thus treated. Such favorable reports, as I have been able to find, are (to me) not in the least convincing, for exophthalmic goiter is a disease very erratic in its course from day to day and almost from hour to hour. That in most cases thyroid therapy is harmful cannot be questioned. That it is even occasionally useful (except when the patient showns signs of hypothyroidism) has not in my opinion been demonstrated.[10]

Obesity

The striking increase in metabolism, caused by administration of thyroid and the clinical observation that obesity, more or less pronounced, was a common feature in myxedema and other conditions of hypothyroidism, naturally suggested that thyroid might prove useful in the treatment of obesity. Barron appears to have been the first to test this clinically, and he and others quickly demonstrated that in many cases of obesity the administration of thyroid was followed by a prompt and decided loss in weight, often amounting to as much as 2 to 10 pounds

treatment involves much more than this the reader desiring to familiarize himself with Rogers' views is referred to the section on Exophthalmic Goiter and its treatment and to Rogers' own communications.

[9a] That the overstimulated but inefficient thyroid might, under the assumed conditions, elaborate an incomplete, toxic secretion is conceivable. The patient might thus simultaneously manifest hypothyroidism and thyrotoxicosis. Janney has elaborated this idea.—R. G. H.

[10] Personally I have never felt that I was justified in giving thyroid to a case of exophthalmic goiter (or to one presenting any signs of hyperthyroidism) unless the patient had passed temporarily or permanently into a stage of hypothyroidism or into a stage, in which there were at the same time signs of both hypo- and hyperactivity of this gland (if such ever occur). Consequently I have myself never obtained bad results from its administration in this disease. In a limited number of my own cases, which, on the advice of other physicians, had taken thyroid, I have never seen beneficial effects, which, in my opinion, could with any probability be attributed to this part of the treatment, and some of the patients were certainly harmed by it.

the first week, and from 10 to 35 or more pounds in the course of two or three months. Yorke Davies found that in patients, previously kept for some time on a restricted (obesity) diet the administration of thyroid increased by two or three times the rate of reduction in weight. While for a time clinical reports of this new method of treatment were unanimously and unreservedly favorable, before long less favorable reports appeared. Attention was called to unfavorable effects on the general health, to the fact that much of the loss in weight was the result solely of loss of water from increased diuresis, and to a by no means infrequent failure to secure any considerable or permanent reduction in weight. Abuse of the thyroid treatment of obesity by physicians prescribing too large doses, or failing to properly observe their patients, its exploitation by vendors of obesity cures, and self-administration by patients all combined to bring the treatment into disrepute, so that many clinicians unreservedly condemned it as useless or harmful. Following this swing of the pendulum there ensued a period of careful investigation which has made it possible to reach relatively definite conclusions as to the clinical utility and value and also as to the limitations and harmfulness of thyroid treatment of obesity.

Various investigations of the influence exerted by thyroid feeding on the metabolism of obese patients have given apparently contradictory results. In almost all of Magnus Levy's (*b*) (*c*) cases there was a negative effect on the nitrogen balance and no constant increase of basal metabolism, and when this latter effect was produced it was so slight that he concluded that the loss in weight produced was not due to increased oxidation of fat, but chiefly to increased destruction of protein and increased excretion of water. Other investigators also reached similar unfavorable conclusions, and attention was called to the occasional production of glycosuria, of marked nervous symptoms and, relatively rarely, of a condition of hyperthyroidism. Opposed to these unfavorable findings and opinions were the demonstrations by Zinn and Schiödte that the nitrogen balance of obese patients may be kept positive, if the diet contains sufficient protein and the thyroid dosage be not too large. As von Noorden and others (notably v. Bergmann) have shown that there is a type of obesity (constitutional obesity) in which the basal metabolism is abnormally low, due, according to von Noorden, to hypofunction of the thyroid, the administration of thyroid in these cases appears to be justified. and clinical experience has corroborated this view.

In using this method it is well to remember that, as shown by v. Bergmann, the increased protein destruction often does not manifest itself before the second or third week of treatment, and that a sufficient amount of protein in the diet will counterbalance this. Both Locke and Hoyten have found that thyroid is especially useful in reducing the weight of middle aged women, especially in those who have passed the menopause.

My own experience has been that, after excluding clearly hypothyroid cases, my best results have been obtained in cases of young and middle aged women in whom obesity was associated with scanty or irregular menstruation or with amenorrhea.

Unquestionably, if carelessly used in the treatment of obesity, thyroid can and does do serious damage, but the writer believes that its harmfulness (when properly used) has been exaggerated by too many authorities and that its cautious, carefully controlled administration has been of distinct value in a considerable proportion of the cases in which he has employed it in conjunction with other measures. The most brilliant results will be obtained in cases of the so-called constitutional obesity or in cases of obesity showing other signs of hypothyroidism. However, it is my belief that in any case of obesity, not responding well to diet, purgation and exercise, it is well to make a trial of thyroid feeding while continuing the same régime. This should be done cautiously, starting with one grain three times a day and increasing gradually until favorable or unfavorable effects are noted. If three to five grains thrice daily do not exert an unmistakable influence, I do not persist in the administration, as I fear the harmful effects of larger doses. In a goodly proportion of my own cases the results have been most gratifying and I have seen no bad results. I have, however, seen cases of obesity treated with thyroid before coming under my observation, in whom it would appear that harm (not very serious) had been done, and it must not be forgotten that the claim has been made that abuse of thyroid feeding in the treatment of obesity has caused the Basedow symptom complex to develop (von Notthaft). The physician or patient, however, who expects a satisfactory reduction in weight from thyroid medication unassisted by other approved measures, will rarely fail to be disappointed, and whoever attempts thus to obtain favorable results runs a grave risk of doing serious harm.

Empiric and Symptomatic Thyroid Therapy

Thyroid treatment of the various diseases and disturbances of function, as discussed in the preceding sections, may be considered true organotherapy (substitutional therapy), as there are good grounds for assuming that they are all (certain types of obesity excepted) more or less entirely due to deficiency or disorder of the thyroid function. In addition to those already discussed, there are a very considerable number of other diseases and conditions in which the value of thyroid administration has been more or less definitely established, but in which hypo- or dysfunction of this gland has not been demonstrated (and in some of which not even assumed). Here the employment of this treatment rests largely on an empiric basis, i. e., on the effects which have been obtained in clinical trial, for which

in certain instances no thoroughly adequate explanation has yet been furnished, while, for the beneficial effects obtained in others of this group, a more or less sufficient explanation is furnished by the known physiological effects of thyroid administration.

Rheumatism (Articular and Muscular).—The frequency with which patients with myxedema suffer from so-called rheumatism and the beneficial effects exerted thereon by thyroid therapy have suggested that even a minor degree of hypothyroidism may play a causative rôle in certain cases of arthritis [11] and that thyroid therapy would prove beneficial under these conditions. As in an overwhelmingly large proportion of cases of arthritis there is an element of infection, and, as there are grounds for believing that the thyroid gland exerts at least some influence on the processes of immunity,[12] it is not illogical to assume that even a slight degree of hypothyroidism will render an individual abnormally susceptible to joint infection, and that in such a case thyroid, by augmenting the formation of antibodies, would assist in overcoming the infection. According to fairly numerous clinical reports (among others, of Hertoghe, Leopold-Levi and Rothschild), thyroid administration has often proven strikingly beneficial in "rheumatic" patients, and that, too, in patients not otherwise suggesting hypothyroidism. Such observations by no means indicate that all cases of so-called rheumatism will be benefited by thyroid therapy, as some enthusiasts would appear to believe, but "rheumatic" symptoms, especially in the middle aged and elderly people, respond to it favorably often enough to justify its trial, in conjunction with other measures of known value, such as removal of infectious foci. I am convinced that I have greatly helped some of my patients with subacute or chronic arthritis or with "muscular rheumatism" by giving them thyroid in doses of ½ to 1 or 2 grains daily.

Diseases of the Bones (Rickets).—Among other conditions in which hypothyroidism has been thought to play a causal rôle is *rickets,* but it is reasonably certain that thyroid dysfunction is only occasionally, if ever, responsible for the development of this disease. From the results of feeding thyroid to rachitic children as reported by various authors (see von Jauregg, loc. cit., p. 140) it is extremely doubtful whether this is of any value whatever except in cases which are also hypothyroid, in which case one may well attribute the favorable changes noted to the glandular therapy. Thyroid administration is indicated in rachitic cases only if there be a certainty or a suspicion of hypothyroidism.

In *delayed union* following fractures, thyroid therapy has been em-

[11] In this connection much interest attaches to a case reported by Acchioté, in which arthritis developed in a woman, whose thyroid became atrophied as a result of X-ray treatment, and whose "rheumatism" was promptly cured by thyroid administration.

[12] See discussion on use of thyroid in infectious diseases (p. 103).

ployed by Hanan and others, who have reported favorable results (for literature, see Bayon).

Tetany.—Although theoretically there are no grounds for assuming that a deficiency of the thyroid hormone is in any degree responsible for the development of tetany, thyroid feeding was rather extensively employed at one time and thought to be, at least occasionally, of some value in the treatment of this condition. As the majority of the favorable reports on this use of thyroid date back some time and are opposed by a number of unfavorable reports, it would appear that it is at best of but slight value (von Jauregg, Pineles (*b*)).

Mental Diseases.—Among the many claims made by certain writers on organotherapy is one to the effect that thyroid therapy is of great value in the treatment of insanity of various types. Although the view that thyroid is in any sense a specific or even a frequently valuable remedy for insanity is almost universally rejected by psychiatrists of to-day, there was a time, not so remote, when the greatest enthusiasm prevailed in regard to the use of thyroid in the treatment of various types of mental disease, and when many psychiatrists were convinced that in it they had found a remedy of great therapeutic value. MacPhail and Bruce were the first to claim and to publish reports [13] indicating that a large proportion of cases of insanity of different types were either curable or amenable to great improvement by thyroid treatment. As a result of these reports many other alienists were led to give this method a very extensive trial. As is almost universally the case with a new method, while the early reports indicated its great value, later ones showed a falling off in the percentage of cures and improvements claimed.

In 1900 Mabon and Babcock reported 50 cured, 94 improved and 364 unimproved in 508 cases collected by means of a circular letter, and 116 cured, 143 improved and 226 unimproved in 485 cases collected from the literature, and, in their own series of 61 cases, 12 cures and 16 improvements. From their own experience and from the study of the results reported in the 1,032 cases collected by them, these authors were convinced that the administration of thyroid extract must have actually produced changes in the brain cells in order to bring about the marked improvement noted in some of these cases, and they published a number of conclusions which, in slightly abbreviated form, follow: 1. The dose varies from 5 to 25 (!) grains 3 times a day. 2. For best results, confinement to bed for the whole period of treatment and for a week afterwards is essential. 3. The treatment should be continued for at least 30 days. 4. Failure of a first treatment may be followed by success in a second, third, or even later repetition. 5. Best results are obtained in acute mania, melancholia with prolonged attacks, puerperal and climacteric insanities (which show a high

[13] Bruce's own figures, in a series of 87 cases, were 42.9 per cent cured and 21.9 per cent improved!

percentage of spontaneous recoveries, J. T. H.), stuporous states, and primary dementia. 6. To obtain a favorable result, it is not necessary to cause a high temperature reaction. 7. Physical benefit resulted in most cases even without improvement of mental state. 8. The proportion of relapses was less than in those cases cured by other methods.

Such optimistic views were for a time shared by many other alienists, Middlemass (quoted by von Jauregg, who appears to agree with him), for instance, having expressed the opinion that it was not justifiable to consider a psychosis incurable until the thyroid treatment had proven unsuccessful. Unfortunately the experience of the years that have passed since this treatment of mental cases was introduced has failed to corroborate the opinion that thyroid treatment is so generally applicable or so frequently successful as these earlier observers believed, and it is noteworthy that except in Great Britain and America it was never generally adopted. The consensus of opinion to-day is that thyroid administration is occasionally beneficial [14] in patients with melancholia and stuporous conditions, and that it may be useful and should be tried in cases of insanity of various types if the patients show evidence of hypothyroidism.[15] The doses used to-day are, however, very much smaller than those of twenty years ago, and are the same as those generally employed in the treatment of hypothyroidism.

Quite recently thyroid therapy has again been advocated as useful or curative in *dementia præcox,* Raecke and others believing that various reports indicate its probable value.[16]

Epilepsy.—From time to time it has been thought by various observers that there was a more or less frequent relationship between epilepsy and dysfunction of the thyroid (Claude and Schmiergeld), and that thyroid therapy had produced remarkably beneficial results in the treatment of this disease (Bolten, Leopold-Levi and Rothschild). It would be hard to define the status of thyroid therapy in epilepsy better than has been done by Dercum (*a*). "In a given number of instances the physiological level of the patient may be distinctly raised by the administration from time to time of small doses of thyroid extract, say from 1/8 to 1/4 grain three times a day, seldom more." Naturally there can be no question of the

[14] No mention of any such general application of it or of the use of such massive doses as advocated by MacPhail and others has been found in recent text-books or journals.

[15] Post-mortem examination of cases of insanity show a rather large proportion of abnormal thyroids. Peabody's series of 50 autopsies is fairly typical in showing over 22 per cent with marked chronic interstitial thyroiditis and lesser degrees of the same in 32 per cent.

[16] There is some evidence suggesting that dysfunction of this gland may be more or less frequently present in cases of this type of mental disease, Dercum and Ellis having found the thyroids small in 7 out of 8 autopsies of cases of dementia præcox, but, while Peabody found anatomical changes in the thyroid gland of three cases of long standing, he found no demonstrable changes in these glands in two cases of briefer duration.

propriety of and benefit obtainable by the administration of thyroid to epileptics, who are also hypothyroid, for it is a rule, to which there are few exceptions, that whatever improves the general health of these cases also exerts a favorable influence on the epileptic seizures.

Enuresis.—Early in his studies of patients suffering from myxedema and milder degrees of hypothyroidism, Hertoghe (*a*) (*b*) called attention to the frequent occurrence of enuresis in these cases and to its cure by thyroid therapy. A little later and quite independently, Williams (*a*) was led to try it in cases with this complaint and reported twenty-five cures in the twenty-six thus treated. The remarkable thing about Williams' experience was that in most of these cases there was none of the usual signs of hypothyroidism. While from time to time Waller and others have reported cure or amelioration of this distressing symptom from the administration of thyroid, and although it is frequently referred to in textbooks, the treatment would not appear to have become popular. The doses used should be small, from ½ to 2 grains per diem. Too large doses seem to aggravate the enuresis.

Constipation.—In the discussion of the effects of thyroid therapy in myxedema and other forms of hypothyroidism, mention has been made of the frequency with which these patients suffer from constipation and of the cure of this symptom by thyroid administration. These experiences have suggested the trial of thyroid as a means of treating constipation in other cases not obviously hypothyroid, but it is extremely doubtful if its use for this indication is justifiable, unless there be a suspicion or certainty that the patient is hypothyroid. Waller has found it very useful in pediatric practice, and often serviceable in diarrhea!

Deafness.—The improvement in hearing resulting from thyroid therapy in myxedematous subjects, who so frequently are more or less deaf, led Vulpius to investigate its effects in cases of deafness of other causation. While he reported benefit in a considerable proportion of his cases, others who followed him (for literature, see von Jauregg, loc. cit., p 150) have not expressed themselves so favorably. According to Vulpius, the most amenable cases were those with hypoplastic middle ear changes. In old cases with sclerotic changes no favorable results were obtained, but in cases of this kind in the moderately youthful the treatment was often somewhat beneficial. The absence of any reference to thyroid therapy in recent textbooks and articles dealing with the treatment of deafness indicates that to-day otologists in general have little or no belief in its value except in cases of hypothyroidism.

Asthma.—Levy and Rothschild and others have maintained that asthma is at least occasionally a manifestation of hypothyroidism and have reported beneficial results from thyroid treatment. While, to me at least, it is very improbable that asthma is often of thyroid origin, there are certain reasons why it does not seem improbable that administration of

thyroid may exert a favorable influence on it.[17] That except in hypothyroid individuals it will prove more efficient here than the administration of iodids, I do not believe.

Infectious Diseases.—In organotherapeutic literature, especially that issued as propaganda, reference is frequently made to an important rôle played by the thyroid in immunity processes, with at least an implication that thyroid administration may therefore be useful in patients suffering from various infectious diseases. Thus far at least the evidence that this is so is by no means conclusive, although it is fairly conclusive to the effect that impairment of the thyroid function does lessen the powers of resistance. This has been shown by the almost universal experience that thyroidectomized animals and hypothyroid patients are abnormally susceptible to infections, and by Koopman's observation that in hypothyroid rabbits the antibody formation was slow and imperfect and that under the influence of thyroid it became normal. Fassin's (*a*) (*b*) (*c*) claim that after thyroid administration to normal animals the immunizing properties of their sera are augmented has not to my knowledge been confirmed, but would indicate that this effect is exerted not only in hypothyroid but also in normal animals. I know of no clinical observations that would indicate that in individuals with normal thyroids the administration of thyroid substance increases their immunity reactions.* Until such clinical evidence has been brought and in no uncertain form, it would seem unwise to assume that thyroid therapy will have such an effect.

Syphilis.—Although as long ago as 1893 reports were made of the successful employment of thyroid in the treatment of syphilis and although since then similarly favorable results have from time to time been reported by various authors (see von Jauregg, loc. cit., p. 152), these communications appear to have attracted little attention and syphilographers generally have not been inclined to accept it as a useful agent in the treatment of this disease. Wagner von Jauregg, however, as the result of his own clinical observations and because of certain theoretical considerations, considers that, in some cases at least, thyroid administration is distinctly more beneficial than that of iodids. He also believes that the ingestion of thyroid distinctly increases the tolerance to mercury, and states that certain of his cases, which had been unsuccessfully treated with mercury and iodids, were promptly and decidedly benefited when thyroid was substituted for the iodid.[18] He urges that in cases of syphilis, which have shown

[17] The well established utility of iodids in these cases appears as I have pointed out elsewhere, best explained as follows: By the administration of iodids the thyroid is stimulated to greater activity and this leads to increased sympathetic tone, which, by its influence on the bronchial muscles, tends to prevent bronchial spasm. A similar effect may be expected from thyroid administration.

[18] At the post-mortem examination of one of these patients, who died of an intercurrent infection, the thyroid was found in an advanced stage of atrophy.

* See Addendum, p. 150.

themselves refractory to the usual mercury and iodid therapy, treatment with mercury, iodid, and thyroid be given a trial.

While according to our present views iodids do not owe their value in the treatment of syphilis to their action on the thyroid there is at least one established fact which lends support to the view that thyroid therapy may be a useful adjuvant, at any rate occasionally, to other antiluetic therapy. This is that syphilis by no means rarely attacks the thyroid gland and that in such cases there may develop hypothyroidism with its various consequences, among which a lessening of the power of resisting infections [19] is perhaps of especial moment in this connection. These views of von Jauregg's certainly appear worthy of remembrance, and thyroid therapy would seem worthy of trial in recalcitrant cases of syphilis, especially if there be any evidence that the thyroid has been affected.

Nephritis.—Remarkably beneficial results from thyroid therapy in cases of nephritis have been claimed by Percy (*a*) (*b*), who in 1912 and 1913 reported a considerable number (35 in his first communication) of severe cases all of whom were strikingly benefited. I cannot find any later article containing further reports with greater detail as promised by him, but in 1916 Phipps reported that in several cases of severe nephritis (but not in all) he had obtained marked improvement, due in his opinion to the administration of thyroid. Percy's average doses of 20 grains per day, and those of Phipps of from 5 to 15 grains daily are so large that it is surprising that Percy observed hyperthyroidism develop in only one case.

The reports as made by these two writers are not such as to compel acceptance of their views, for, without medicinal treatment, very sick nephritics often show surprising changes for the better, even such diminution in blood-pressure as reported by Percy and such improvement of renal function as Phipps observed. For me the known facts as to the effects of thyroid feeding on renal function and metabolism in no way explain the results claimed. Consequently, I must await further reports before acknowledging the connection between the thyroid therapy and the improvement reported.

Affections of the Skin.—The abnormality of the skin and other epidermal structures in myxedema and other types of hypothyroidism and the manner in which this is benefited by thyroid therapy naturally suggested that thyroid dysfunction might be at least partially responsible for, and that thyroid therapy might prove of value in the treatment of various skin diseases. To a limited extent at least clinical trial has justified these views.

Psoriasis was the disease in which such trial of thyroid therapy was first made and numerous cases of cure by it have been reported, but dermatologists to-day are well agreed that this treatment is successful in only a small proportion of cases of psoriasis and that the affection is not

[19] See discussion of use of thyroid in infectious diseases (p. 103).

directly caused by dysfunction of this gland.[20] McLeod considers it especially useful in chronic cases and states that the successful dose is sometimes small and sometimes large and can be determined only by trial.

On account of the superficial similarity of *scleroderma* and *ichthyosis* to the condition of the skin in myxedema these affections have also been looked upon as possibly of thyroid causation and treated accordingly. The results have been variable, the failures outnumbering even partial successes. In *eczema* results have been very doubtful except in cases otherwise suggestive of hypothyroidism and the same may be said of the results in cases of *alopecia.* Although successful thyroid treatment of juvenile warts, keloid, lupus vulgaris, urticaria, pruritus, and various other conditions of the skin have been reported from time to time, the connection between the treatment and the cures reported is doubtful.

The unsatisfactory state of our knowledge as to the significance of the thyroid and status of thyroid treatment in dermatological practice is well exemplified in recent articles by McLeod, Foerster, and Pulay. It would appear that it is occasionally useful in a moderate number of different affections as noted above, but that its greatest usefulness is in its administration to patients suffering from various types of skin disease, who are also hypothyroid. McLeod states that in dermatological practice it is best to start with small doses which may be increased if no results are obtained.

Blood Dyscrasias.—Thyroid medication has also been reported as beneficial in *hemophilia,* as in Pugh's case, in hemorrhagic conditions, such as *purpura,* and in *epistaxis,* in which Waller states that, as it sometimes retards and sometimes accelerates coagulation, it may prove either useful or harmful, but to me it seems extremely doubtful that it exerts any influence in such cases.

The Parathyroid Gland

Our knowledge of the functions and significance of the parathyroid glands has been derived from three sources, the results of their extirpation in animals and man, post-mortem findings in cases of tetany, and observation of the effects of implantation of parathyroid tissue and of administration of parathyroid substance to parathyroidectomized animals and to human cases of tetany.

From observation of the effects of extirpation it has been learned that the removal of a sufficiently large portion of the glandular tissue is regularly followed by the development of tetany with fatal outcome. The

[20] A case has been reported by Ewald (quoted by von Jauregg) in which psoriasis developed in a patient who was taking large doses of thyroid as a part of his obesity cure.

implantation experiments have shown that successful grafting almost invariably prevents the development of tetany (or at least lessens its severity in cases where it occurs in spite of the grafting) or, in cases when tetany has already developed, relieves the symptoms or ameliorates their severity. Both in the laboratory and the clinic the effect of administration of preparations of the gland has been exceedingly variable, but it would appear that at times at least effects are obtained qualitatively similar to those obtained by implantation (vide infra), although quantitatively much less pronounced. The results of post-mortem examination have been relatively meager and have contributed to our knowledge in only a moderate degree, but, as far as they go, they are confirmatory of the conclusions reached by other methods.

Parathyroid therapy has been employed in a number of conditions and diseases with more or less reported benefit, but here, as elsewhere in the domain of organotherapy, much uncertainty still prevails as to its real value and the correct indications for its application. From various sources there are reports of its more or less successful use in tetany (post-operative and idiopathic), paralysis agitans, eclampsia, epilepsy, and chorea, but it is only in the treatment of tetany that parathyroid therapy rests on a firm and rational basis.

Tetany.—The relationship of parathyroid insufficiency and tetany having been demonstrated both by the extirpation experiments of various investigators and by clinical observations, the next logical step was the investigation of the effects of the administration of preparations of this gland to parathyroidectomized animals both before and after tetany had resulted.[21] The results obtained by various observers were for the most part disappointing and varied decidedly. In cats, in which tetany had resulted from complete or partial parathyroidectomy, Biedl (quoted by Pineles (*b*)) could observe no favorable effects from the administration of preparations of this gland, and Pineles, who administered such preparations, orally, subcutaneously and intraperitoneally had a similar experience, finding that such therapy exerted no favorable influence whatever in the tetany following removal of the parathyroids. MacCallum and Voegtlin (*b*) and Marine (who gave to their dogs as much as 100 fresh glands per diem) reached the conclusion that the oral administration of parathyroid was useless. On the other hand, a number of other observers have reported that the tetany could be checked by feeding parathyroid or by injection of its extracts (Carlson (*a*)). From these experimental studies the conclusion may be drawn that, after complete removal of all parathyroid tissue, the administration (by any route) of parathyroid prep-

[21] In the earlier stages of the study of experimentally induced tetany, at a time when it was believed that tetany was the result of removal of the thyroids, it was the preparations of the thyroid which were thus administered. Curiously enough certain observers observed beneficial effects therefrom but the majority obtained only negative results.

arations can very rarely, if ever, prevent the development of tetany or cure it once it has developed. However, some of the observations recorded would appear to show that when not too large an amount of parathyroid tissue has been removed the administration (by various routes) of parathyroid can prevent the development or lessen the severity of the tetany so that life is prolonged until the remaining glandular tissue is able to hypertrophy sufficiently to meet the necessities of the case, or until, in some other manner, the organism accommodates itself to the parathyroid insufficiency. These experimental studies have thus furnished a basis for the hope that in human tetany also parathyroid administration could be useful to a limited extent.

That a much greater therapeutic effect is exerted by implantation of parathyroid grafts was quickly demonstrated in the laboratory. While Schiff (*c*), in 1884, by implantation of thyroid tissue (which must have also contained parathyroid tissue), was able to prevent tetany in thyroidectomized dogs, it was not until later, when the parathyrogenous origin of tetany had been recognized, that grafting of parathyroid tissue was attempted as a possible method of preventing or curing experimental tetany. Such experiments, conducted by a large number of different investigators, promptly showed that successful grafts exerted an unmistakably beneficial effect in parathyroidectomized animals, although the results obtained were very variable and often somewhat disappointing. That the implanted parathyroid tissue is actually responsible for the claimed therapeutic effects was perhaps most definitely demonstrated by Leischner, who found that in animals, in which tetany had been prevented or cured by implantation of the extirpated glands, removal of the grafts one or two months later was followed by tetany. It has been the experience of almost all observers that these grafts rarely if ever persist for more than a relatively short period.[22] Halsted (*a*) (*b*) (*c*) believed that the grafts will "take" only if there be a parathyroid insufficiency with the organism suffering therefrom, but that they will not take if the parathyroid tissue remaining and that implanted taken together are able to prevent any insufficiency. The various laboratory investigations indicate clearly that, in experimentally induced tetany, implantation of parathyroid tissue has a definite therapeutic effect similar in kind to but much more powerful than that resulting from the administration of preparations of the gland. It appears, however, that even the successful implantation of one or several glands does not act as a certain preventative of or cure for tetany unless a certain amount of functioning parathyroid tissue has escaped removal. This indicates that grafted parathyroid tissue is able to compensate only for a subtotal insufficiency (and then only for a time), thus enabling the animal to

[22] Christiani, however, was able to demonstrate microscopically their persistence for two years in rats and for five years in cats in which he had reimplanted parathyroid tissues in their original sites.

survive long enough for the parathyroid remnants to hypertrophy sufficiently or for some other unknown compensating mechanism to develop.

As all the known facts indicate the essential similarity of tetany, as experimentally induced in the laboratory, and of the tetanies of various causation observed clinically, there existed good grounds for the expectation that, in human cases of tetany also, parathyroid therapy would produce results similar to those produced by it in the laboratory, and this expectation has been in large measure justified by clinical experience. In the clinic as in the laboratory the results from oral and hypodermic administration of various parathyroid preparations have been in the main uncertain and disappointing while those obtained by implantation have been more certain and valuable. Both successes and failures following the administration of parathyroid substance to cases of tetany of various types have been reported by various authors in fairly equal proportions.[23] Among those reporting more or less striking successes are Halsted (1907, 1909), Bircher (*b*) (1910), Marinescu, Vassale, and quite recently Haas; while among those reporting failures are Frankl-Hochwart, Pineles (*b*), Escherich, and Arntzenias. In Halsted's case, which has been reported with considerable detail, the beneficial results of the parathyroid therapy appear to have been incontestable and may be quoted as typical of the kind and degree of benefit which may result from parathyroid administration in cases of this type. In his patient, who was "suffering greatly from subtetanic hypoparathyroidism as a result of strumectomy," tetany was averted and the status thyreoprivus was made endurable by the feeding of parathyroids, by the injection of Beebe's nucleoproteid, and for almost a year by administration of calcium lactate. The dose given at first was large, six dried (later fresh glands were used) ox glands every three hours and the effect was "almost instantaneous and marvelous." After a few days this dose was reduced to one gland thrice daily.

Escherich's case of tetany in a nursling, aged 5 months, ended fatally, although energetically treated with Vassale's parathyroidin; Frankl-Hochwart observed no benefit from the same preparation used in five cases of idiopathic tetany, nor did Pineles in three cases to whom horse parathyroids were fed; the last named author also quotes Rensburg and Rey as having seen only aggravation of the disease in cases of infantile tetany treated by administration of parathyroid preparations. Haas observed no effects whatever in four cases to which he fed fresh and dried glands in doses up to 100 grams at a dose; the cases, as shown by their fairly satisfactory response to calcium lactate, do not appear to have been of extreme severity.

In attempting to form an estimate of the clinical value of the administration of parathyroid in cases of tetany, two factors must be well

[23] As failures are much less frequently reported than successes, this would indicate that the failures have been more numerous.

weighed. One is the great difference in the severity of these cases and the extreme difficulty of forming a correct prognosis. The other is the great variation in the results (both in clinic and laboratory) reported by various observers. From the available data it appears to me that while definite and incontestable proof of the efficiency of such therapy may still be lacking, the evidence is strongly suggestive that in some cases at least a certain amount of benefit may result from its employment. In view of this conclusion and as there is practically universal testimony that the oral administration of parathyroid is harmless, I believe that in mild cases it should be tried, either alone or in conjunction with other therapy, but that in more severe cases, as so little is to be expected from it, it should be used only as an adjuvant to other measures, including implantation. It should be used also when it is impossible to have an implantation carried out. As neither laboratory nor chemical experience has shown that the therapeutic effects of injections are superior to those obtained by oral administration,[24] and as various parathyroid preparations contain more or less protein, oral administration is to be preferred on account of the usual objections to injection of foreign protein.

The greater efficiency of parathyroid implantation (as compared with that of its administration), so clearly demonstrated in the laboratory, has also manifested itself in the clinic. While it does not always entirely relieve the symptoms, prevent the development, or avoid the fatal outcome of tetany, the reports of its successful employment are constantly increasing in number so that there can no longer be any question that it is the method of choice in the treatment of this disease.

Von Eiselsberg in 1907 was the first to report the successful relief of a case of tetany through implantation of a parathyroid graft. His patient was a woman of forty-two, who, as a result of a total strumectomy, had suffered from chronic tetany for twenty-five years, and in whom thyroid and parathyroid feeding had been without effect. Following the implantation of one parathyroid gland the convulsive attacks became less frequent and the other symptoms of the latent tetany were decidedly ameliorated. In the same year Pool transplanted five parathyroid glands, removed from cadavers, into the abdominal wall in a case of tetany parathyropriva, with prompt and complete relief of the condition. Similarly favorable results were soon afterwards reported by a considerable number of surgeons. In 1919 Borchers (*a*) (*b*) was able to collect from the literature twelve cases of post-operative tetany thus treated, with five temporary and three permanent successes. To these he added two successful cases of his own, to which may be added two successes reported by Thierry and one case reported in 1920 by Landois in which the implantation of three parathyroids was followed by only temporary benefit, the patient dying

[24] While various authors have claimed that injections are more efficient the evidence presented is by no means conclusive.

later of tetany, also two cases of Jaeger's, in which the benefit obtained was but slight. Hunt quotes Krabbel as reporting two successful results from transplantation in patients suffering from idiopathic tetany. Complete relief was secured in one of these, a girl, who suffered from tetany only during her menstrual periods, while the other, a man with genital hypoplasia, was reported as relieved.

While the great majority of those recording their experience with this method of treatment have reported successes from its employment, there are also reports of more or less complete failure and doubtless many more failures have remained unreported. In spite of the fact that occasionally transplantation fails to afford any relief and that often the condition is only ameliorated and not cured, it would appear that the results obtained by many surgeons have proven beyond dispute that this operation holds out the best chance for the cure or amelioration of tetany and that it has often proven lifesaving in cases in which other methods of treatment had been ineffectual. It is at least doubtful whether in a case in which there is total parathyroid deficiency even numerous grafts will be able to entirely relieve the condition.

Parathyroid Insufficiency.—Cases of this type must either be very rare or else are almost never recognized. The only one found by me in the literature is one reported by Hertz, which is of especial interest here because of the apparently specific effect exerted by parathyroid substance administered orally. The dosage employed was ¼ grain of dried ox parathyroid four times daily, which was later reduced to once daily.

Paralysis Agitans.—Favorable effects from administration of parathyroid to patients suffering from paralysis agitans have been reported by Berkeley (*a*) (*b*) (*c*) in this country and Lundborg in Sweden, and by a number of others, among them Alquier, and quite recently by Gautier, who considers its effects incontestable. Berkeley (1916), after eleven years' experience, believed that parathyroid feeding is not a cure, but that 60 to 70 per cent of the patients, who have tried it faithfully for three to six months, have been greatly benefited, the progress of the disease having been arrested or markedly retarded. He advises one or two doses daily of 1/50 grain of the purified acetic acid extract (Berkeley and Beebe) which may be given orally or hypodermically. If the dried gland preparations are used, Sajous advises a daily dose of 5 to 7 capsules, each equivalent to ½ grain of the fresh gland. The experience of the majority of clinicians with this remedy appears to have been like that of Block, in whose hands it failed to produce any effect. Dercum (*b*) states that in doses of 1/20 to 1/10 grain thrice daily it is temporarily of benefit by diminishing the tremor but that it loses its effect in ten days to two weeks. The evidence of its value in this disease is certainly questionable but, as most observers [25]

[25] Pineles (*b*) states that Roussy and Clunet observed an aggravation of the symptoms in two of their cases under this treatment.

report no harmful results from its use, there appears to be no objection to its trial. In my own cases I have never seen any good or bad effects follow its administration.

Other Convulsive Conditions.—In *eclampsia* the beneficial action of parathyroid is claimed by Vassale (1905), who also reports that two cases of *epilepsy* were controlled by it. Naamé also reports encouraging results from its use in a number of cases of epilepsy, and quite recently in this country Knox has reported fairly good results in thirty cases treated by the administration of dried parathyroid glands and of calcium lactate. Knox's initial dose of two grains thrice daily is increased each month by two grains per dose. *Chorea* is another disease in which the administration of parathyroid has been attended with reputed benefit chiefly in the hands of Italian physicians (for lit. vide Harrower (*a*)). There is no satisfactory evidence that either eclampsia, epilepsy, or chorea is in any way causally related to the parathyroid, nor is there any evidence that parathyroid substance possesses any pharmacodynamic powers which would be useful in these diseases. Therefore, its use in these diseases is purely empiric and its efficiency or the lack of it must be demonstrated by the observed results. Certainly the clinical reports thus far are not sufficiently great in number or convincing enough in character to inspire confidence in the claims made.

The Hypophysis Cerebri

In spite of an enormous amount of investigation both clinical and experimental, the organotherapeutic employment of posterior pituitary preparations has been established as a useful measure in only a relatively limited field, although many enthusiasts have advocated and are advocating its use in a large number of different conditions. Among those conditions in which its organotherapeutic powers have been demonstrated with more or less certainty, are various conditions attributed to hypofunction of this portion of the gland, such as the late stages of acromegaly, pituitary obesity (including well defined cases of dystrophia adiposogenitalis),[26] faulty development of the sexual organs, various disorders of the menstrual functions, and diabetes insipidus.[27]

The individual viewpoint must for the present determine whether or not the favorable influence exerted by posterior pituitary medication in

[26] That dystrophia adiposogenitalis or pituitary obesity is due solely to hypofunction of the pars posterior is more than doubtful; many authorities (among them Blair Bell (*c*), 1919) believing that in them dysfunction of the pars anterior also plays a rôle, and by far the more important one.

[27] If the contentions of Camus and Roussy (*a*) and of Houssay be correct, that it is trauma of the region of the third ventricle (not trauma nor injury of the pituitary) which causes experimental polyuria, then the use of pituitary extract in this disease must be looked on as hormonotherapy rather than as organotherapy.

certain cases of exophthalmic goiter is to be considered as due to organotherapeutic or hormonotherapeutic action.

Dystrophia Adiposogenitalis and Pituitary Obesity.—The treatment of these conditions by administration of posterior pituitary gland will be deferred to a later section, because of the uncertainty as to the rôle played in them by the different portions of the gland, and because in most of the cases treated by administration of pituitary substance preparations of the whole gland have been used.

Acromegaly.—In the late stages of this disease, where hyperfunction has been succeeded by hypofunction, the administration of posterior pituitary substance can be of benefit if there be present symptoms of hypofunction of the pars posterior. Ordinarily in such cases the use of preparations of the whole gland would be preferable.

Disturbances in the Functions of the Female Genital Organs.—Posterior pituitary therapy in this type of case is treated elsewhere.

Diabetes Insipidus.—Francisco, in 1913, appears to have been the first to employ posterior pituitary extract successfully in the treatment of this condition. His experience was promptly corroborated by numerous observers, especially by Motzfeldt (*a*) (*b*) (*c*) (1917-1918), who has made an extensive clinical and experimental study of this matter. At the 1920 meeting of the Society for the Study of the Internal Secretions, Barker reported successes in a considerable number of cases. In the discussion following this paper, Engelbach, Rowntree, and others, also reported almost uniform success.[28]

In most of the cases benefit is obtained only by hypodermic or intramuscular injections, but Motzfeldt (1918) reports one case markedly benefited during two years by the oral administration of from 2 to 7 fresh ox glands per diem; and Rowntree, in the discussion at New Orleans, reported that in one mild case the oral administration of 4 ox glands per diem controlled the polyuria fairly well, and that in another case the extract administered rectally would hold it in check for 3 or 4 hours. It has been the experience of the various observers that as a rule the injection of 1 c.cm. of the 10 per cent extract controls the polyuria for from 6 to 10 hours. However, the effect varies within wide limits, as little as 1 c.cm. injected every fifth day having sufficed in one case (Rowntree), while in others satisfactory relief could be obtained only by the injection 2 or 3 times daily of 1 c.cm. As the injections often cause considerable pain and discomfort, it is wise in most cases to attempt to control only the nocturnal polyuria. In some patients the cathartic effects of the injections are extremely inconvenient. In such cases smaller dosage more frequently administered may be tried. The effects obtained are almost

[28] In view of Abel's (1919) claim that histamin is one of the active principles of this gland, some interest attaches to Rowntree's report that this substance failed to exert any influence in cases of diabetes insipidus in which it was tried.

always only temporary, although Barker states that treatment along these lines can lead to cure or to such improvement that the dose may be diminished.

Exophthalmic Goiter.—Salmon's conception of the rôle of the pituitary in exophthalmic goiter led Renon and Delille to investigate the effects of pituitary administration in this disease, and as they reported beneficial results, it has also been used for this indication by a number of others, many of whom have reported favorably as to its value, among them being Hofstätter (*b*), Pal (*c*) (1915), and Claude, Baudouin, and Porak.

Hofstätter reports in detail the results in 15 women, who had almost without exception failed to improve under the methods of treatment ordinarily employed. He used preparations both of the whole gland and of the posterior portion, administered either orally or hypodermically, but found the injections decidedly more efficient. The usual duration of treatment was four weeks, 12 injections of 1 c.cm. of the extract being given three times a week. His conclusions (which appear well sustained by the cases reported) are that the treatment adopted proved almost without exception to be of distinct benefit. The exophthalmos and goiter were only slightly influenced, or not at all, but the tremor, vasomotor symptoms, hyperidrosis, psychic symptoms, asthenia or lack of energy, and digestive disturbances were almost uniformly lessened or entirely relieved. With a very few exceptions the menstrual disturbances (present in all these cases) were promptly corrected, and the body weight increased. The tachycardia also was usually favorably influenced. Pal (1915) reports 16 cases thus treated. Of 9 cachectic cases, 7 gained weight, and at the same time the restlessness, the tremor, and usually the hyperidrosis, diminished. The exophthalmos was little (if at all) affected, while the tachycardia improved only slowly, did not disappear entirely, and returned when medication was discontinued. The thyroid often increased in size during treatment. Some of these cases, originally so sick that operation was considered inadvisable, showed such improvement under treatment that they were later operated on successfully. In one case oral administration was followed by striking improvement, but in the others it was necessary to give the drug hypodermically. Dosage was 0.25 to 1.0 c.cm. pituitrin. Claude, Badouin and Porak (1914) conclude that the pituitary is not a specific in this disease, but that it exerts a favorable influence in some cases. They report that the injections were often immediately followed by a very striking lessening of the heart rate. Borchardt (*b*) (1914) cites a number of other clinical reports by various observers in which favorable results were recorded, but there are not lacking reports of cases in which it was tried and failed.

Hofstätter, without reaching any definite conclusions, devotes considerable space to an attempt to explain the favorable results obtained by himself and others. He offers several hypotheses for consideration:

(1) that symptoms due to dysfunction of the pituitary (damaged by the thyrotoxicosis) are benefited by the pituitary administered; (2) that the results are due to the beneficial effect on the ovarian functions, which are so commonly deranged in this disease; (3) that, as claimed by Pal, the pituitary exerts a restraining influence on the abnormal thyroid activity; (4) that the relief of at least some of the symptoms is due to purely pharmacodynamic actions of the posterior pituitary extract.

This method of treatment appears worthy of trial in inoperative cases of exophthalmic goiter, especially in patients in whom the menstrual function is deranged.

It is quite in accord with the present uncertain status of organotherapy that similar favorable effects have been reported as following the administration of anterior pituitary substance (Harrower (*b*) (1917), Hoppe (*a*), Richter). Inasmuch as experimental evidence is fairly conclusive to the effect that the anterior pituitary and the thyroid are closely related physiologically and that they can to some extent at least function vicariously, it is hard to believe that administration of one of these glands can exert a favorable influence on a condition caused largely (if not entirely) by overactivity of the other.

Hypophyseal Hormonotherapy

The powerful pharmacodynamic actions exerted by posterior pituitary substance on various functions have led to its trial in a large number of conditions; in some of which it has failed completely, while in others its value has been clearly demonstrated, and in still others is not yet determined.

Disorders of the Circulation.—The striking effects of posterior pituitary substance on the circulation, as observed in the laboratory, naturally led to its early and wide trial in this field.

In *cardiac diseases,* both acute and chronic, it has been used by many authors, but there is much difference in their conclusions as to its value. Rénon and Delille reported that both oral and hypodermic administration of extracts of the anterior (!?) and posterior portions exerted a favorable influence in various types of cardiac diseases, especially in cases of myocarditis.[29] They report as evidence of its favorable influence in these cases increased diuresis and slightly increased blood-pressure.

Arrhythmias were not influenced, but in several cases tachycardia

[29] Laboratory studies appear to have proved definitely that the anterior portion of the gland contains no substance which could act beneficially on the circulation. This claim of these authors that anterior pituitary substance can produce such effects in the clinic must therefore be received very skeptically; and at the same time it raises a doubt as to the reliability of their conclusions concerning the value of the administration of extracts of the posterior lobe. Moreover, it has been the almost universal experience that posterior pituitary substance administered orally is inert or nearly so.

was controlled after other therapy had failed.[30] While other authors have expressed views similar to those of Rénon and Delille, these do not seem to have been accepted by the majority of clinicians. In a considerable number of my own cases of circulatory disease, injections of pituitrin have appeared to exert little if any favorable influence on the circulatory function other than an indirect one due to their effect in the relief of abdominal distention (see below), for which they have no superior.

There are numerous clinical reports that the administration of posterior pituitary substance has produced good effects on the circulation in the *sepsis of infectious diseases, peritonitis,* and *infected wounds.* Among others who hold such views is Delille, who used it in a series of twenty-eight cases of typhoid, of which two died, while another had intestinal hemorrhages. This author states that "in all these cases the institution of pituitary therapy was followed more or less rapidly and to a greater or less degree by a rise in the blood-pressure, slowing of the pulse, increased diuresis, and improvement of the general condition." A shortening of the period of convalescence was also claimed. In spite of such reports, it would seem that posterior pituitary substance, when administered subcutaneously to typhoid patients, must by its action on peristalsis increase the danger of hemorrhage and perforation. In personal experience with cases of other infections, in which the typhoid state had developed, my own failure to observe anything more than an occasional very slight and temporarily beneficial effect on the circulation, leads me to advise against injections of pituitary extract in cases of typhoid fever; and I am unable to believe in its efficiency when administered orally. However, if these injections do not cause either hemorrhage or perforation, they may well prove useful by prevention or relief of the tympanites which so often aggravates the condition of typhoid cases.

In other septic conditions there are not the same objections to the administration of posterior pituitary substance, and the view is quite widely held that here it frequently exerts a beneficial action on the circulation. Blair Bell (*c*) (1919) states that "in sepsis of a serious character such as may occur in appendicitis or puerperal infection, infundibulin (a posterior pituitary extract) is of the very greatest value." He injects 0.5 c.cm. of infundibulin intramuscularly twice daily as long as the symptoms are acute. Schmidt has shown that in the clinic, pituitrin raises the diastolic pressure in febrile conditions. Borchardt (*b*), after reviewing the literature, reaches the conclusion that in infections the administration of posterior pituitary substance is clearly indicated only in

[30] Every clinician of sufficient experience is aware of the difficulty of determining whether the cessation of one of these paroxysms following any line of treatment is an instance of *post hoc* or *propter hoc.* However, there is pharmacological evidence that the injection of extracts of this gland may directly depress cardiac muscle and in this way it is possible that such would exert a favorable influence in tachycardia.

these very exceptional cases in which the toxemia has damaged the heart. Here this treatment may raise the blood-pressure, strengthen the heart, slow its rate, and improve the quality of the pulse. My own experience with this method of treatment of circulatory failure in infections has left me very skeptical as to its value.[31] There is need of further investigation along experimental and especially along clinical lines.

Shock.—Mummery and Symes appear to have been the first to advocate the administration of pituitary substance in shock. Since that time it has been rather extensively tested, and many surgeons have reported favorably as to its value. Blair Bell (*c*) (1919) considers that while it is not a specific, it is useful both as a prophylactic measure and also after shock has developed. He recommends its injection in doses of 1 c.cm. of the 20 per cent extract of the pars posterior. He stresses the relatively long duration of its effects on the blood-pressure, stating that he has seen this effect maintained for as long as 8 hours after administration. Experience in the great war has led many others to a similar conclusion. The British Medical Research Committee recommended it as of considerable value. Among my own surgical colleagues I find a practically unanimous agreement with this view. However, the available literature leaves the impression that further careful observation, both in clinic and in laboratory, is needed before it will be possible to form a correct estimate regarding the real value of, and the indications for, this drug in the treatment of shock.

To obtain the effects on the circulation it must be administered hypodermically or intramuscularly in full doses (0.5 to 1.0 c.cm. of the 20 per cent extract), and the frequency of repetition must be determined by the effects. Murray (*d*) and others advise intravenous injection where the indication is very urgent.

Renal Disease.—The diuretic action observed in the laboratory aroused the hope that a similar action might be exerted in cases of renal disease. While in the earlier literature there are a number of papers reporting favorable results from the administration of pituitary substance to nephritics and cardiorenal patients, more extended clinical experience has failed to justify a belief in the efficiency of such therapy.

Alimentary Canal.—In paralytic distention of the stomach or intestine, and in general abdominal distention the value of posterior pituitary extracts (first advocated for this indication by Blair Bell and Hick in 1909) is well established. Experience has shown that, after various other measures have failed, an injection of 0.5 to 1.0 c.cm. of the 20 per cent extract often brings about vigorous peristalsis in cases where this con-

[31] In a very considerable number of cases of pneumonia, where I have used pituitary extracts to meet another indication, careful observation of the effects on the circulation has not convinced me that these are beneficial.

dition develops after laparotomy, or in the course of peritonitis or of infectious disease. My own experience along these lines has been mainly in its use to relieve the abdominal distention which so often develops in the course of pneumonia. Here such injections have almost uniformly secured the desired result, so that in my own practice it has become the routine method of combating meteorism in infectious disease.[32] In the meteorism of typhoid fever, fear of causing hemorrhage or perforation has held me back from its use, but I am not certain that this timidity is justified. While Musser has reported good results in the treatment of chronic atonic constipation by the oral administration of extracts of the whole pituitary or its posterior portion, in acute conditions the drug must be given by needle. In order to obtain more certainly the desired effect on the intestines, Blair Bell (*c*) (1919) advises that a turpentine enema be given 10 minutes after the pituitary extract has been injected. In cases of paralytic distention of the stomach, he advises washing out the stomach ten minutes after giving the injection. An absolute contraindication to this use of the drug is the existence or even the suspicion of any form of obstruction, or perforation, or of acute appendiceal trouble. Barker (personal communication) has observed striking relief in episodic marked distention in a case of Hirschsprung's disease.

Bladder.—The pressor effect exerted on the bladder by posterior pituitary extract has led to its administration in paretic conditions of the bladder. Miller cites several authors who report that these are especially valuable in postpartum and postoperative retention. From several of my surgical colleagues I have reports of their successful employment under such conditions. Blair Bell (*c*) (1919) reports that in his experience the action on the bladder of even large doses is uncertain, and that in postoperative paresis he has never seen it cause emptying of the bladder, unless the bladder was fully distended, and that even then the extract often failed to produce the desired result.

The successful employment of the extract in nineteen cases of *enuresis* has been reported by Mikhailow. Ten of his cases were children from 5 to 10 years of age, who were cured by doses of 0.2 to 1.0 c.cm. of pituitrin given by injection once a week for three or four weeks. Cure of enuresis in cases presenting signs of hypopituitarism has been repeatedly reported as one of the beneficial effects of pituitary therapy.

Bronchial Asthma.—Bronchial asthma is another condition in which good results are claimed from the use of posterior pituitary extract, usually in combination with epinephrin, as first suggested by Weiss. While there seems to be little or no pharmacological basis for this method of treatment, its value is attested by a number of observers.[33] Bourgeois

[32] The experience of Miller (1916) is directly contrary to this.

[33] When estimating the therapeutic value of this combination, the almost uniformly successful use of epinephrin alone must not be forgotten.

reports that the insertion into the nares of pledgets soaked with equal parts of hypophysin (a posterior pituitary extract) and 10 per cent novocain gives marked relief with no untoward effects. In a rather limited personal experience with this combination (of epinephrin and pituitrin), I have seen no better results from it than were obtained in the same cases by epinephrin alone. The remedy is used hypodermically, and the dose recommended by Weiss is 0.8 mg. of suprarenal extract with 0.04 gm. of posterior pituitary extract.

Spleen.—Blair Bell (*c*) (1919) states that his colleague, R. J. M. Buchanan "has treated successfully a serious case of splenomegaly by the oral administration of an extract of the whole gland."

Obstetrics and Gynecology.—The obstetrical and gynecological uses of posterior pituitary extract will be discussed in another section.

Anterior Portion of the Pituitary Gland

In contrast to our extensive knowledge of the pharmacology of the posterior portion of the pituitary, is our extremely meager knowledge of that of the anterior portion.

Chemistry.—According to Robertson (*a*) (1916), one [34] at least of the active principles (the growth-controlling one) is a lipoid fairly soluble in water, and in certain mixtures of alcohol and ether, which contains nitrogen and phosphorus in the ratio of 4:1, and yields inosite on hydrolysis. This substance (or mixture of substances), to which he has given the name *tethelin,* is not affected by trypsin nor lipase (Schmidt and May). It is rapidly decomposed under the influence of heat and moisture, and when treated with barium hydroxid yields a substance exerting on the uterus and the blood-pressure an action similar to that of posterior pituitary extracts. Robertson believes that tethelin rapidly undergoes decomposition in the alimentary tract and in this liability to destructive change he sees a probable explanation of the rather disappointing therapeutic results which have thus far been obtained by most observers from oral administration of anterior pituitary substance. He believes that the commercial preparations are unsatisfactory for hypodermic administration on account of the difficulty in freeing them of proteid without largely destroying their activity. It is evident that our knowledge of the chemistry of the pars anterior is still very incomplete.

Pharmacodynamic Effects.—No immediate pharmacodynamic effects on the various functions have been observed following either oral administration or injection of anterior pituitary preparations.[35] Prolonged feed-

[34] We do not know whether there is more than one active substance.

[35] Robertson states that in rabbits the intravenous injection of 150 mgm. of tethelin (the amount contained in 15 whole ox glands) produced no immediate effects other than a slight and transient rise in blood-pressure and an increase in the amplitude of the heart beat.

ing produces striking effects on metabolism, growth and development. These are fully discussed elsewhere and may here be summarized as follows: (a) Either retardation or acceleration of growth depending on the age and stage of development of the subject; (b) shortening of the period of complete sexual development; (c) expediting of the awakening of the sexual instinct.[36]

Cushing (*b*) (1912), working with dogs, and Smith (*a*) (*b*) (*c*), using tadpoles, demonstrated that in the laboratory at least orally administered anterior pituitary substance is absorbed sufficiently to produce some organotherapeutic (constitutional) effects. In addition to these more general effects Robertson (*b*) has also shown that administration of anterior pituitary substance accelerates the healing of wounds. Schmidt has shown that tethelin injections produce no antigenic or other effects which contraindicate their clinical use.

Organotherapy with the Anterior Portion

In general, the results of the organotherapeutic employment of anterior pituitary substance have been rather disappointing and unsatisfactory. This is to be explained partly by our relatively incomplete knowledge of the normal and pathological physiology of this portion of the gland, which is responsible for an all too frequent inability to recognize and correctly interpret the clinical syndromes resulting from disturbances of its functions. Doubtless also the lack of suitable preparations for therapeutic employment, and insufficient knowledge of the correct dosage and proper method of administration have militated against securing some at least of the results which may be attainable. In spite, however, of the present rather unsatisfactory status of this phase of organotherapy, experimental and clinical studies have already shown that there is a field, by no means small, in which the administration of an anterior pituitary substance produces unmistakably useful results. Unfortunately in an all too large proportion of the observations (both clinical and experimental) made on the effects of pituitary organotherapy, preparations of the whole gland have been used. Consequently it is often extremely difficult or impossible to determine whether the results obtained by observers were due to the therapeutic action of the anterior portion or that of the posterior part or to the combined action of both portions, and there still remains much to be learned of the organotherapeutic powers of anterior pituitary substance. Theoretically at least this should be useful in cases suffering from *dysfunction or hypofunction of the pars anterior.*

[36] In view of the reputed efficiency of anterior pituitary medication in hyperthyroidism interest attaches to the demonstration by Hoskins and Hoskins (*c*) that feeding of anterior pituitary substance to thyroidectomized tadpoles brings about metamorphosis just as does feeding of thyroid substance.

Dystrophia Adiposogenitalis and Pituitary Obesity.—In dystrophia adiposogenitalis and pituitary obesity (which by many are considered to be due chiefly or entirely to hypofunction of the pars anterior, although Cushing and others believe that in their case there is also hypofunction of the pars posterior), pituitary therapy has been employed with some success, which may be looked upon as at least in part resulting from an organotherapeutic action of the pars anterior. Unfortunately in the majority of the cases reported in the literature preparations of the whole gland have been used. Although pituitary therapy has often proven unsuccessful in these cases, favorable results from such treatment have been reported by a number of clinicians.

Von Cyon appears to have been the first to obtain favorable results from administration of pituitary substance to a case of this type, incorrectly diagnosed by him as acromegaly. Cushing (*b*) in certain of his cases obtained results varying from slight to marked amelioration. Beck reports twelve cases in which administration of anterior or whole pituitary substance, usually combined with thyroid and sometimes with ovarian extract, caused a redistribution of the fat and an increase in the function of the sex glands besides a correction of some of the anomalies due to hypoplasia of the genitalia.[37] Engelbach (in William Tice's "System of Medicine"—in preparation—and in a personal communciation to the author) has frequently seen strikingly beneficial results from the administration of anterior pituitary substance—either alone or combined with posterior pituitary substance—to patients presenting signs of deficiency of the anterior lobe, or of both lobes. In such cases Engelbach has occasionally obtained effects from the oral administration of these substances; but he believes that when thus administered even in large doses (15 to 30 grains) they are not particularly effective. From the hypodermic administration of anterior pituitary preparations (such as antuitrin), he has obtained strikingly beneficial results. The dosage depends on the degree of hypofunction of the anterior lobe, the correct amount being determined by the therapeutic effects, such as decreased muscular and mental fatigue, restoration of normal menstruation, return of libido, and development of a general sense of well-being. For establishing the correct dose, Engelbach has found that the therapeutic results have been of more value than either basal metabolism determination or carbohydrate tolerance tests. In his experience there have been no untoward effects from anterior lobe extracts when given by subcutaneous, intramuscular, or intravenous injection.

[37] In view of the different opinions as to the rôle played in this disease by the different portions of the pituitary some interest attaches to Dziembowski's report that the daily injection of 1.1 c.cm. of hypophysin (that is, posterior pituitary) caused loss of weight and return of libido in a patient with dystrophia adiposogenitalis, who had previously been treated without benefit by the administration of thyroid, suprarenal, and testicular extracts.

The last method has been employed by him in a few cases in which as much as 2 or 3 c.cm. of antuitrin have been given daily.

Timme also has reported marked benefit from the oral administration of anterior pituitary substance, either alone or in the form of preparations of the whole gland. His report is based on a series of cases considered by him as examples of pluriglandular (thymus, adrenal and pituitary) dysfunction or hypofunction. Here the outstanding clinical feature is great muscular fatiguability, often associated with temporal headache, delayed genital development, menstrual disturbances, and anomalous growth. It was especially in the cases with deficient genital development that anterior pituitary feeding proved beneficial. Of the whole gland preparations, Timme uses fairly large doses (gr. ii to gr. iii t.i.d.), while occasionally for a week or two at a time he gives daily injections of 0.5 to 1.0 c.cm. of pituitrin. He reports that pituitary feeding alone produces highly satisfactory results in almost all of these patients, the fatiguability and headache disappearing, and the case going on to cure. In the older and more advanced cases, relapse is likely to occur if treatment be discontinued.

Osteomalacia.—In osteomalacia, in which success has also been claimed from posterior pituitary therapy, good results have been claimed also from the feeding of anterior pituitary extract (Pal (*b*), 1912).

Impotence.—Impotence in the male is another condition in which anterior pituitary has been administered with claimed benefit. Stellwagon reports cures in several cases in which desiccated anterior lobe was administered. As other methods of treatment were also employed, there is reasonable ground for questioning the rôle played in the cure by organotherapy.

Epilepsy.—Anterior pituitary therapy in epilepsy is briefly considered elsewhere (p. 123).

Organotherapy with the Whole Pituitary

For reasons sufficiently well known, it is even yet often impossible to determine whether it is dysfunction of the pars anterior, or of the pars posterior, or of the whole gland, which is responsible, wholly or in part, for the symptoms and pathological conditions presented by many cases. Consequently, preparations of the whole gland are very often administered in the attempts to secure therapeutic results. In some cases, it is true, one may by careful study obtain evidence that the whole gland is at fault, in which case the employment of the whole gland preparations is indicated, but all too often one is left in doubt whether one or both portions are involved.

Among the conditions in which, with claimed benefit whole pituitary preparations have been used are (in addition to those mentioned in the

preceding secretion) pituitary headaches, the late stages of acromegaly (stage of hypofunction), tumors of the pituitary, epilepsy, and the psychoses of adolescence.

Pituitary Headache.—The frequency with which recurring headache of a peculiar type (bitemporal, very intense, described by the sufferer as "boring") was present in patients presenting other conditions suggestive of pituitary disturbance, led Pardee to administer pituitary substance to a series of seven such cases. The results obtained were most gratifying; and in all the cases making up this series there was marked amelioration or cure of the headache. The dose employed by Pardee was ¼- to 2-grain tablets 3 times a day by mouth. Glassberg reports that the daily administration of 8 grains of pituitary extract cured severe headache of over two years' duration in a patient presenting various signs of hypopituitarism. Dalché reports relief of headache from administration of 0.1 gm. dried extract of the whole gland 2 to 4 times daily in a case in which "an endocrin upset had induced congestion of the pituitary." Timme and many others have noted that in many cases of dyspituitarism relief of headache followed pituitary medication.

Acromegaly.—In acromegaly, when the disease has reached the stage of hypopituitarism, benefit of some of the symptoms at least may be expected from the administration of whole gland preparations. Cushing (*b*) (1912) cites one acromegalic who experienced in this stage subjective benefit from the daily ingestion (for some months) of the enormous dosage of 100 grs. of the whole gland preparation. Borchardt (*b*) states that symptomatic relief has followed pituitary therapy in cases of acromegaly which have been reported by a number of observers, although a still larger number have failed to obtain such results. He quotes Renon and Delille as reporting harmful effects in a case of acromegaly, which was evidently still in the stage of hyperfunction.

Tumors of the Pituitary.—Examples of beneficial effects ascribed to pituitary therapy, are 3 cases of pituitary disease with temporal neuralgia and gradually increasing blindness reported by De Schweinitz and How. In these cases administration of pituitary extract and thyroid combined with mercury rubs [38] caused steady and progressive improvement of vision. Elsberg and Krug also have reported a case showing signs of hypophyseal pressure, in which after failure of decompression, pituitary injections improved the failing vision.

Epilepsy.—In epilepsy also good results have been reported from pituitary administration, among others by Tucker (*b*) (1919). In sixty-three out of two hundred consecutive cases, this author found what he considered evidence of pituitary disease. After eliminating thirty-five of these because of other conditions, he decided that twenty-eight of them were cases of pure hypopituitary type, chronic or transitional. Adminis-

[38] In none of these cases were there other signs of syphilis.

tration of 10 to 20 grains per diem of preparations of the whole gland (to a few cases with high blood-pressure anterior gland only was given) was followed by striking improvement in all but two cases. In the discussion of this report of Tucker's, Sterne stated that he had had no results whatever from administration of anterior pituitary to a large number of epileptics and that in several hundred cases of epilepsy treated by administration of the whole gland the results had been nothing like those reported by Tucker. Hoppe (*b*) saw no benefit from anterior pituitary feeding in an epileptic considered by him to be a case of hypopituitarism. In 1913, Cushing (*c*) reported that pituitary feeding ameliorated epileptic attacks in two cases of dystrophia adiposogenitalis.

A single case of apparent cure of epilepsy by the daily administration of 8 to 10 grains of pituitary extract has been reported by Joughlin, and Spears reports apparent cure following the administration of 2 grains of anterior pituitary 3 times a day in a patient who from his sixth to his twenty-eighth year had an average of four attacks per diem.

While the examination of the skulls of epileptics by the X-ray is stated by certain observers to show abnormalities of the sella in a large percentage of cases (McKennan, Johnson and Henniger), Munson reached a different conclusion as the result of his investigations. There is certainly no sufficient evidence so far that disease of the pituitary is the general cause of epilepsy. In view, however, of the reported benefit from pituitary therapy in epilepsy, it seems advisable to look for evidence of pituitary dysfunction in epileptics, and when such is found to make a trial of pituitary preparations.

Psychoses of Adolescence.—In the psychoses of adolescence Tucker (*a*) (1918) reports beneficial effects from feeding preparations of the whole gland or of its anterior portion. According to Ludlum and Corson-White, pituitary therapy caused improvements in a group of cases, clinically dementia præcox of the hebephrenic type, but presenting signs of hypopituitarism such as lowered blood-pressure, subnormal temperature, scanty crines, undeveloped genitalia, muscular asthenia and adiposity. Angell also reports (with no details) several good results from feeding whole pituitary to several cases of dementia præcox.

It is regrettable that none of these authors give any details as to dosage or duration of treatment and that Ludlum and Corson-White do not state whether the preparations administered were those of the whole gland or of the anterior or posterior portions.

The Corpus Pineale

While it is now generally conceded that the pineal gland is an organ of internal secretion and that administration of pineal substance causes in young animals acceleration of growth and sexual maturity (McCord

(*c*)), up to the present no one has succeeded in proving that pineal substance can exert any therapeutic influence.

The claims made by Dana and Berkeley that, in a number of defective children at the Vineland institution and from New York public schools, its administration for a period of some months brought about an improvement of mental condition, have been deprived of most if not all of their value by the later report of Goddard, who followed some of these cases for over a year and concluded that the Vineland experiment had had only negative results. Negative results have also been reported by Block.

The Suprarenals

Pharmacodynamic Actions of Epinephrin

In the chapters on the physiology and pharmacology of the suprarenals a detailed account of the actions of epinephrin is given. The data that pertain more particularly to the therapeutic possibilities of this drug will be summarized briefly at this point. The pharmacodynamic properties of epinephrin have been well characterized by Langley and Elliott in the statement that its peripheral effects are everywhere essentially the same as those produced by the stimulation of the sympathetic nerves of the tissues involved.[39] Perhaps the most striking demonstration of this fact is found in the different reaction of the same organ in different species of animals. For example, in certain species epinephrin causes relaxation of the bladder, in others contraction.

Seat of Action.—Various investigations, but particularly those of Langley, on its effects after nerve degeneration, have placed the seat of action in the histologically undemonstrable so-called intermediary receptive substance where nerve structure ends and muscle structure begins.

Circulatory Action.—Intravenous injection of epinephrin is followed promptly by a striking rise in the blood-pressure and almost immediately thereafter by slowing and irregularity of the heart. The rise in blood-pressure is, under normal conditions, mainly due to the general vasoconstriction, but some of it is due to the increased force and extent of the cardiac contraction which brings about, at least at the beginning, an increased cardiac output. The slowing of the heart is the result of increased vagus tone, which probably is chiefly or entirely the result of the increased blood-pressure, although direct stimulation of this center cannot be excluded. The irregularity is due to variation in vagus tone or to premature (ectopic) contractions of the heart, or to both of these factors.

[39] Its lack of effect on sweat glands is an apparent contradiction to this general law. While anatomically the secretory nerves supplying these glands are sympathetic, according to their pharmocodynamic reaction they belong to the parasympathetic portion of the vegetative nervous system.

All these effects pass off rapidly, the blood-pressure falling within a few minutes to its original level, or even lower, while the heart first goes back to its former rate and then as a rule exceeds it. This acceleration is due to the fact that the accelerator action persists longer than the rise in blood-pressure, and is no longer overcome nor masked by the vagus stimulation. The fall in blood-pressure below its original level is the result of a late vasodilation.[40] The stimulation of the accelerator endings is best studied on the isolated surviving mammalian heart, where it manifests itself by a striking increase in the rate, force, and extent of the contractions. This effect manifests itself in vigorously beating, as well as in feeble exhausted hearts. In the intact mammal, large doses frequently cause premature (ectopic) ventricular contractions, and under certain conditions ventricular fibrillation. This latter is especially liable to occur under light chloroform anesthesia.[41] Rothberger and Winterberg found that in dogs epinephrin caused the same electrocardiographic changes as accelerator stimulation.

The behavior of the different arteries under the influence of epinephrin has been intensively studied by many observers. Using segments of isolated arteries, Langendorff found that epinephrin caused contraction of all the arteries of the body, with the exception of the coronary vessels, which are dilated. His findings have in most particulars been confirmed by other observers. In the intact mammal, however, conditions are not so simple. Numerous investigations, notably those of Hoskins (*c*), and of Hartman (*b*), have shown that with ordinary doses there is constriction of the splanchnic and cutaneous vessels, and dilatation of the vessels of the lungs and voluntary muscles.

The clinical use of epinephrin in the treatment of hemoptysis renders it desirable that we should know how this drug affects the *pulmonary circulation.* Studies on the isolated artery by Langendorff and the perfusion experiments of Plumier and of Wiggers (*a*) (1909) show that these arteries follow the general rule of responding to epinephrin by contraction. However, Brodie and Dixon found that very small doses caused dilation, and Hartman and Hoskins, using the intact mammal, with ordinary intravenous doses, also found a vasodilating effect. Schäfer and Lim, using intravenous and intra-arterial injections, found in rabbits a

[40] Cannon and Lyman (*a*) (1912-13) have found that in cats very small doses usually cause a fall in the blood-pressure. In a series of clinical observations on the effects of oral administration of epinephrin, I have occasionally seen a slight but distinct fall in blood-pressure without any preceding rise. It is possible that this fall is analogous to that observed by Cannon and Lyman.

[41] Levy (*a*) (*b*) (*c*) and Lewis found that in cats, which had been sufficiently deeply anesthetized by chloroform, subsequent light chloroform anesthesia so affected the heart muscle that accelerator stimulation caused the development of ventricular fibrillation. As the action of epinephrin on the heart is identical with that of accelerator stimulation, it is not surprising that injection of epinephrin brings on this condition. The clinical importance of this fact must not be overlooked when using epinephrin in threatened chloroform death.

primary rise followed by a fall in pulmonary and systemic blood-pressure, attributed by them mainly to action on the arteries. In cats they usually obtained a rise of pressure in both systems due chiefly to increased cardiac output, but small doses were followed by a fall in both systems, which must be due to arterial dilatation. In dogs there was a marked rise of pressure in both systems, attributed largely to increased output. It is evident from the above that our knowledge as to the changes in the pulmonary circulation produced by epinephrin is very unsatisfactory. As in the treatment of hemoptysis, epinephrin is almost always given hypodermically, its effects must be similar to those produced by very small doses given intravenously. The laboratory evidence, therefore, would indicate that when thus administered it dilates the pulmonary vessels.

Locally applied to mucous membranes and open wounds, or injected under the skin, epinephrin causes marked vasoconstriction, which is usually followed after a time by marked vasodilatation.

Blood.—Laboratory workers early noticed that in experiments in which epinephrin was injected the blood frequently coagulated in the cannulæ, indicating an increased coagulability of the blood. That this is actually so was later demonstrated by Richards and Vosburg, and by Cannon and Mendenhall.

Respiratory System.—The most striking and clinically most important action of epinephrin on this system is its power of preventing or relaxing spasm of the bronchial muscles (Januschke and Pollak). Following intravenous injection of moderate doses, there is evidence of stimulation of the respiratory center, while after large doses this center is depressed. In laboratory experiments large intravenous doses, or smaller ones frequently repeated, often cause pulmonary edema.

Alimentary Canal.—The local astringent effects may be obtained in the mouth, esophagus, stomach, and rectum. When injected intravenously, the motor functions of stomach and intestines are inhibited, just as if the splanchnic nerves were stimulated. It is of interest that doses insufficient to affect the blood-pressure produce this effect, but the practical importance of this fact is lessened because of the evanescence of this action. Yukawa found that oral administration markedly increased the secretion of hydrochloric acid, while Rogers, Rahe, and Ablahadian found that this secretion was diminished after intravenous injection of suprarenal extract.

Uterus.—The effect of epinephrin on the uterus varies with different species and with the state of the organ (whether pregnant or not). This variability in its action runs parallel with the varying effect of sympathetic stimulation under like conditions. They both cause powerful contractions of the pregnant uterus, and also (in some species) of the non-pregnant uterus. In the virginal uterus of the cat or dog, on the other hand, epinephrin causes relaxation (Kehrer). Stewart (1912) has shown that in very small dosage epinephrin causes relaxation.

Eye.—In addition to producing local vasoconstriction, epinephrin, by stimulation of the sympathetic nerve endings, causes retraction of the eyelids and exophthalmos; and, if it penetrates sufficiently into the inner eye, mydriasis results from stimulation of the nerve endings of the dilator pupillæ. Loewi found that in pancreas diabetes the repeated instillation of epinephrin solution (1-1000) into the eye caused well marked mydriasis, although in normal human beings this is not the case. The same effect is produced in cases of hyperthyroidism and other states of abnormal excitement of the sympathetic nervous system. With further observation, the diagnostic significance of this eye test has been found to be of little or no value.

Voluntary Muscle.—The contraction of normal muscle is not affected, but its relaxation is greatly slowed as by veratrin. In fatigued muscle (frog's gastrocnemius), epinephrin temporarily restores the power of contraction. Later investigations threw doubt on these views, but the most recent one by Guglielmetti fully confirms them. In Addison's disease, Dupaigne and Langlois demonstrated ergographically that the prolonged administration of suprarenal substance increased muscular power, and Trerotoli obtained similar effects from hypodermic administration of epinephrin. This finding appears significant in view of the reported favorable influence exerted by suprarenal medication on the asthenia of Addison's disease. Mention should be made also of the fibrillary contraction of voluntary muscles in the shivering which often accompanies the systemic action of epinephrin, although it is quite possible that this shivering is an indirect result of cutaneous vasoconstriction.

Secretions.—The *tears, saliva,* and *bile* are increased by epinephrin. In the case of the last, it would appear that it is not so much an increase of secretion which is caused, as it is an increased excretion resulting from contraction of the large bile ducts, and perhaps of the gall-bladder also. The sweat glands are not affected, although they are supplied by nerves which anatomically appear to belong to the sympathetic system, but which in their pharmacodynamic reactions behave like parasympathetic nerves.

Kidneys.—The renal vessels are primarily contracted by epinephrin, and later dilated. As a result, urinary secretion is first diminished, later increased. A short-lived polyuria not infrequently follows its hypodermic administration, especially when it is used in combination with cocain.

Suprarenal Glycosuria was first noted by Blum in 1901 and studied intensively by Herter and others, who found that the administration of epinephrin intravenously, hypodermically, or intraperitoneally is, under normal conditions, regularly followed by a temporary hyperglycemia and glycosuria. These are due to an acceleration of the transformation of glycogen into glucose, and also in some degree to lessened oxidation of glucose. The acceleration of the transformation of glycogen appears to be

due not to a direct action on the liver cells, but to stimulation of their sympathetic nerve supply. The lessened oxidation has been attributed to an inhibition of the internal secretion of the pancreas, but for this hypothesis experimental proof is lacking. The study of this suprarenal diabetes led to the elaboration by Falta and others of the Vienna school of an ingenious theory assigning to the suprarenals an important rôle in diabetes mellitus. According to this hypothesis, the suprarenal exerts an inhibitory influence on the production of the internal secretion of the pancreas. However, although it has been shown that epinephrin inhibits the external secretion of this gland, proof is lacking that any similar effect is exerted on its internal secretion.

Metabolism.—The effect of epinephrin administration on nitrogenous metabolism has been the subject of considerable investigation, but there is much discrepancy in the reported results. While a number of investigators report that proteid combustion is increased after its administration (orally or hypodermically), others report no effects on the nitrogen balance, or at times even a nitrogen retention. Tompkins, Sturgis and Wearn report that administered hypodermically epinephrin regularly increases the basal metabolism.

In view of the frequent use of suprarenal preparations in various types of bone disease, and of Sergent's (*a*) belief that they favor recalcification in tuberculosis, their effect on calcium metabolism possesses a certain interest. Quest found that in dogs epinephrin caused a decrease in the calcium excreted by the kidney, but a still greater increase in the amount excreted in the feces, so that the total excretion was increased.

Temperature.—The *temperature* is but slightly affected, sometimes falling, sometimes rising. In man a slight rise (maximum 0.4° C.) occurs more frequently than a fall (Bauer, 1912).

Non-Vegetative Nervous System.—The very striking peripherally induced effects of epinephrin make it very difficult to determine what, if any, direct effects it produces on the central nervous system. Dixon found that locally applied to the frog's cord, it caused greatly exaggerated reflex response, which he attributed to action on the motor cells in the anterior horn. Very large amounts cause motor paralysis, and there are certain observations indicating that a central analgesic action may be exerted by intraspinal injection, or by injection into the carotid (Weber). In spite of such laboratory findings, however, it appears in the highest degree improbable that the doses used clinically produce any important effects on the central nervous system. Epinephrin exerts no action on either sensory or motor nerves in the periphery.

Absorption and Fat in the Body.—Epinephrin is not absorbed through the unbroken skin. Applied to mucous membranes or administered by mouth, it is ordinarily absorbed very slowly and incompletely, if at all. However, by many it is claimed that it is absorbed rapidly

enough from the mouth and stomach to produce systemic effects, and that occasionally, following applications to the nose, conjunctiva, or urethra, marked systemic effects have resulted. The literature is full of statements of the efficiency of suprarenal preparation administered orally. Recently with the assistance of Mr. A. L. Vidrine, Tulane, 1921, I have again investigated this matter. In a series of over forty cases, all of whom reacted unmistakably to the subcutaneous administration of 0.5 c.c., or less, 1-1,000 solution of adrenalin chlorid, doses up to 4 mg. administered orally have with two exceptions failed to produce either objective or subjective effects, unless a fall of about 10 mm. Hg in systolic and diastolic blood-pressure may be considered as an effect similar to that produced in the laboratory by very small doses. That it does not entirely escape absorption when orally administered, is proved by the occasional unmistakable clinical effects, and by its demonstration in the urine of animals to which it had been administered orally (Embden and v. Fürth). Lesné reports that when rectally administered to rabbits its toxic effect approximates that following subcutaneous injection. In one instance, I have seen striking systemic effects follow the insertion of a rectal suppository containing 0.6 mg. adrenalin chlorid, but I have failed in numerous subsequent efforts to get similar effects.

The effects of *subcutaneous injections* are inconstant. Frequently the systemic reaction from ordinary dosage is so slight that it is difficult or impossible of detection, while at times the reaction is quite prompt and well developed. In my own experience, the effects on the blood-pressure and heart rate have oftenest been very slight or entirely lacking, but when thus administered its effects on the bronchi have been unmistakable.

Intramuscular injection usually permits of sufficiently rapid absorption to promptly produce some rise in blood-pressure, acceleration of the heart-rate and other systemic effects. I have once, in a patient later shown to be hypersusceptible to this drug, seen the intramuscular injection of 1.5 mg. adrenalin chlorid followed by effects on the circulation quite comparable to those seen in the laboratory following intravenous injection, namely, rise of blood-pressure from 110 to over 200 mm. Hg with alternately slowed and irregularly accelerated heart action.

From *intravenous* administration there is instantaneous and marked reaction to such a degree that the dose must be very small, well diluted, and slowly injected.

The rapidity with which the effects of a dose of epinephrin pass off appears best explained on the assumption that it is rapidly changed and rendered inert, or that it is absorbed and held fast by various tissues and cells, or that both of these factors are active.

Excretion.—Embden and von Fürth found in the urine a by no means small percentage of the amounts which had been orally administered and there are also a number of other observations which make it probable that

at least traces of epinephrin are excreted in the urine when the drug is administered by other routes.

Acute Poisoning.—As produced in the laboratory, acute poisoning shows great variations in different species. In addition to the circulatory phenomena of high blood-pressure, irregular and violent heart action, and irregularity of respiration, nervous phenomena are prominent. In some species convulsions are followed by coma, in others coma alone develops. In some species the respiration stops before the heart; in others, the heart is the first to fail. Pulmonary edema is an almost constant phenomenon. Post-mortem examination usually shows edema of the lungs. Often there are blood-tinged exudates in various serous cavities, with subpleural, subperitoneal, and subpericardial ecchymoses. The heart is usually in complete diastole and often contains clotted blood. Hyperemia of various organs, and hemorrhages in the suprarenals, thymus, and anterior pituitary are often found. The kidneys show cloudy swelling and at times there is a parenchymatous nephritis.

Chronic Poisoning.—In laboratory animals the most constant post-mortem finding is the arteriosclerosis to which Josué first called attention. This condition is found in animals, not only when the drug has been administered intravenously, but also when the subcutaneous, intraperitoneal, or oral routes have been used. Changes in the inner and median layers of the media predominate. Whether or not such changes can result from the use of epinephrin in human beings is uncertain. Brooks and Kaplan, in an autopsy on a patient treated for months with many epinephrin injections, besides arteriosclerotic changes of the usual type, found also plaques which exactly resembled those ascribed to epinephrin. Somewhat similar reports have been made by others. On the other hand, in numerous cases which had undergone long-continued epinephrin treatment, the post-mortem examination disclosed no such changes. In a case of chronic epinephrin poisoning reported recently by Hoxie and Morris, post-mortem examination failed to show arteriosclerosis of the epinephrin type.

Habituation.—In laboratory experiments, frequently repeated intravenous injections are followed, in some animals at least, by progressively smaller effects on the blood-pressure, although, on the other hand, Kretschmer found that in rabbits it was possible repeatedly to produce the same effect with a constant dose. The many experiments carried out for the purpose of studying the production of arteriosclerosis have clearly demonstrated the development of a rapid habituation, or increased resistance, so that after a few days several times the originally lethal dose can be borne. The habituation, or lessened susceptibility, manifests itself not only in respect to the hemodynamic effects, but also in connection with the glycosuric action. It is also a common clinical experience that many asthmatic patients more or less rapidly develop a tolerance to this drug, but fortunately in many the development of such tolerance is very slow or does

not occur. Thus far no satisfactory explanation for such habituation has been demonstrated. All attempts to show that it is due to formation of an antibody have been unsuccessful. In spite of occasional laboratory observations of incidents suggesting the development of hypersusceptibility, it is improbable that this really occurs. Bossi, however, believes that it does.

Organotherapy with Suprarenal Substances

Suprarenal preparations, including epinephrin, have been and still are employed in a very large and varied field, but up to the present time there is much diversity of opinion as to their value in the treatment of many of the conditions in which their use is recommended. In the light of the still incomplete knowledge of the rôle played by disease or disturbed function of these glands, it is extremely difficult or even impossible to draw a sharp distinction between the employment of suprarenal preparations in conditions where the function of these glands is at fault, and their use to combat various symptoms and conditions not—so far as we know—in any way causally related to disordered suprarenal functions. Among the former may be placed with considerable confidence Addison's disease, and, with much less assurance, acute suprarenal insufficiency, functional suprarenal insufficiency, and Erb's myasthenia.

Addison's Disease.—As the therapeutics of this condition is fully treated in another section of this work, to which the reader is referred, it will be discussed here only in connection with the rôle played in it by suprarenal preparations. Charrin and Langlois, using glycerin extracts of horse and dog suprarenals, were probably the first to employ organotherapy in this disease. Following them, clinicians everywhere have adopted suprarenal therapy as a routine measure in its treatment. While all too often the results have been disappointing, it would appear to be settled that in many cases the administration of suprarenal preparations, or epinephrin, is followed by beneficial and even curative effects. In 1902 Adams was able to collect 120 cases thus treated, in twenty-five of which permanent benefit resulted. The striking improvement of the asthenia has been ergographically demonstrated. Restoration of the blood-pressure to normal, disappearance of the hypothermia, cessation of the diarrhea, and increase in weight are among the other favorable effects noted.

Notwithstanding the many reports of successful treatment of cases of Addison's disease by administration of suprarenal preparations, there are not a few clinicians who are entirely skeptical as to the value of this treatment. Among these may be mentioned Hirsch, who states that there is no cure for this disease, and that organotherapy has not made good. He considers that, among the cases in which cure has been claimed, are many in which the correctness of the diagnosis may be doubted and that in

others spontaneous remissions, which have simulated cure, have been attributed to the treatment employed. However, such absolute skepticism does not appear justified, although in estimating the significance of apparent benefit from organotherapy, it is wise to remember that Addison's disease is almost invariably associated with and caused by tuberculosis. It is, therefore, in many cases difficult or impossible to differentiate between improvement due to the suprarenal therapy and that resulting from the cure or amelioration of the tubercular conditions present.

While the favorable effects reported have followed the administration not only of extracts of the whole gland, but also that of epinephrin itself, extracts of the whole gland seem, at any rate in some cases (Daland, Quincke), to be more effective than the pure alkaloid. Most observers have found that in this disease administration of the drug by mouth is as efficient as, or superior to, its administration subcutaneously. The efficient dosage varies within very wide limits. In Bate's case ¼ grain of suprarenal gland daily was sufficient, while in Suckling's case benefit resulted from gradual increase of the daily dose from 10 grains to 175 grains. In Daland's case 90 grains of suprarenal extract, thrice daily, caused mental and physical weakness, irritability, and insomnia, which disappeared when the dose was diminished, maximum benefit being secured from 35 grains thrice daily.

Attempts to overcome the effects of destruction of the suprarenals by transplantation of the glands have not been lacking. Transplantation of the glands of different species of animals into human beings has brought no favorable results, and in some instances has terminated disastrously, death sometimes following within a few days. Morton reported successful transplantation of a human suprarenal gland in a case of Addison's disease with subsequent marked improvement.

Acute Suprarenal Insufficiency (Acute Hypoadrenia).—It is the opinion of various authors that in numerous patients suffering from a variety of diseases a condition of suprarenal insufficiency develops, which may or may not be accompanied by demonstrable pathologic lesions of these glands. In this country Sajous, and in France Sergent (*a*) (*b*) have been strong advocates of such views. In the opinion of these and many other authors, suprarenal insufficiency develops very frequently in the course of acute infections, during general anesthesia (especially if very prolonged), and also as a result of extremely violent and prolonged muscular effort (for example, in soldiers during the recent great war).[42]

In the *circulatory failure of infectious disease,* suprarenal preparations

[42] That post mortem the suprarenal glands under such conditions frequently show pathologic changes cannot be denied. With our present defective knowledge of the function of these glands, and with the uncertainty whether its hormone normally exerts any important influence on the circulation, it is at least doubtful whether suprarenal insufficiency is (as believed by these clinicians) the sole, or even the chief, cause of the circulatory failure which so often develops in these cases.

have been very extensively employed, and there is much divergence in the reports as to its clinical value. In my own cases, results have been most disappointing, and I believe that such has been the experience of the majority. On the other hand, there are a large number of observers whose experience has convinced them of the very real value of suprarenal therapy under these conditions. Sergent finds in the collapse of infectious disease, trauma, etc., that suprarenal extract, or epinephrin, is very valuable. He believes that the dosage usually given is too small, "that those who give 10 to 15 drops of the 1-1,000 solution orally can expect nothing." He advocates in acute cases hypodermic administration of 2 to 3 mg. of epinephrin per diem in 4 to 6 doses, and in addition gives orally 2 to 4 doses of 0.5 mg. each. In less acute and threatening conditions, he advises its use orally in amounts ranging up to 3 or 4 mg. per diem in 6 to 8 doses. Sajous is convinced of its value in adynamic cases of typhoid fever and other infections. Josuè (1916) assumes that in certain cases of *chronic circulatory failure* the cardiac weakness is due to suprarenal insufficiency (asystole surrénale), and claims striking benefit from the oral administration of extract of the whole gland (1½ grains t.i.d.), or from the injection in divided doses of 1.0 c.cm. of a liquid extract of the whole gland. In my own personal observations of such cases, no benefit has been noted following the oral administration of epinephrin. After its hypodermic administration, there has been at times a very temporary increase in the force of the heart beat, but no permanent benefit even from repeated injections.

In the *collapse of infectious disease* many authors advise much larger doses, up to 6 to 12 mg. per diem, and Kircheim has used as much as 48 mg. in 48 hours. The subcutaneous administration is generally preferred to other methods, but in very acute conditions 0.5 to 1 liter of 1-100,000 to 1-200,000 in normal saline may be given intravenously. Such infusions frequently bring about a very striking temporary improvement, and occasionally at least it is maintained. Of late the trend of clinical opinion would appear to deny or doubt the value of suprarenal medication in this type of circulatory failure.

Shock has also been considered by some as wholly or in part due to acute suprarenal insufficiency. For this hypothesis, proof or even suggestive evidence is completely lacking, and more recent clinical and experimental studies of shock have led to the conclusion that in shock epinephrin is usually useless or even harmful.

A number of experimental and clinical observations suggest that, if not regularly, at least frequently, long continued *narcosis* brings about a temporary suprarenal insufficiency. Whether or not this is the correct explanation for the collapse, which occasionally follows prolonged anesthesia, the administration under these conditions of epinephrin hypodermically or intravenously has often been followed by prompt and per-

manent improvement. (*Post hoc* or *propter hoc?*) When chloroform has been used, however, intravenous injections may be attended with a certain amount of danger, and should be given with great caution. Moreover, the differentiation between such a condition of collapse due to anesthesia and that due to shock would appear to be always difficult and at times impossible. As there is reason to doubt the value of epinephrin in the treatment of shock, it is therefore questionable whether it is good practice to use epinephrin at all in such cases.

Functional Suprarenal Insufficiency (Hypoadrenia).—Although perhaps not definitely demonstrated, it is not improbable that there are individuals in whom the suprarenal glands are to some degree incompetent either congenitally or as a result of exhaustion of these organs through excessive physical exertion. That such is the case has been assumed by certain authors who find in the administration of the whole gland or of its active principle a specific and successful therapy. In general those who recognize this symptom-complex report better results from administration of preparations of the whole gland than from that of the active principle. It does not seem possible at present to form any opinion as to the frequency with which such conditions are capable of recognition, nor of the value of the treatment adopted.

In the collapse with alarming circulatory failure occasionally seen following extreme physical exertion, whether or not this be really due to suprarenal failure, there would appear to be no disadvantage and possibly real benefit from the administration of epinephrin intramuscularly or, with great caution, intravenously.

Erb's Myasthenia.—Although there is no known pathologic basis for assuming suprarenal insufficiency as the cause of this condition, this assumption has been made and, according to Bayer, the administration of suprarenal preparations has been followed by favorable results in a number of cases reported by various observers.

Hormonotherapy (Symptomatic Suprarenal Therapy)

In addition to their employment in conditions more or less certainly due to suprarenal insufficiency, there is a wide field in which suprarenal preparations are administered for the purpose of exerting their pharmacodynamic actions as a means of combating various symptoms and disturbances of function.

Vasoconstricting Action.—Foremost among such therapeutic applications of this drug is the utilization of its local vasoconstricting action. This phase of its use is extended and varied, and here in large measure suprarenal therapy rests on a firm basis, both theoretically and clinically. In connection with its employment to secure such effects at points remote

from the field of application, however, there is still much uncertainty and difference of opinion.

The local vasoconstricting action at the point of application is so widely employed and so well understood that it will be treated here but briefly. One of the greatest and most valuable uses of epinephrin is found in the field of *local anesthesia.* Here it is almost universally injected simultaneously with the local anesthetic agent, as, by its local vasoconstricting action, it prevents the too rapid absorption of the anesthetic, and thus prolongs the anesthetic effects and prevents systemic poisoning. For this purpose very dilute solutions (1-75,000 to 1-150,000) are sufficient. By thus using epinephrin, it is possible to inject amounts of cocain and its substitutes which are many times the ordinary fatal dose under conditions permitting prompt absorption. It must be remembered that the epinephrin should not be added to the anesthetic solution before it is sterilized by boiling, as its solutions do not withstand high temperature.

In the *mouth and upper air passages,* to which it can be directly applied, it is widely used for the control of hemorrhage, to render the mucous membranes and submucous tissues bloodless, and to lessen the hyperemia of inflammation. To meet these indications, it may be applied directly in the form of aqueous or oily solutions in sprays, by painting, or by instillation. In the nares, sprays, instillations and ointments which liquefy at the body temperature, or plugs of absorbent material moistened with aqueous solutions, are most frequently used, although under certain conditions the solution may be injected into the subcutaneous tissues. As such submucous injections are occasionally followed by very marked systemic reactions, they must be employed with caution especially if chloroform is being used. It is to be remembered also that the primary vasoconstriction is almost always followed by a late vasodilatation, which favors the later development of turgescence of the mucous membranes and hemorrhage. In coryza and hay fever, such local applications can give very marked temporary relief. Hemorrhage from the gums is often promptly and permanently checked, and in acute pharyngitis, spraying often gives marked relief of the disagreeable subjective symptoms by lessening the hyperemia. In acute laryngitis and tracheitis the use of aqueous or oily sprays is often of benefit and even the cough of acute bronchitis may occasionally be palliated temporarily by inhalation of finely nebulized oily solutions.

The temporary relief of cases of chronic bronchitis which has followed such inhalations is probably due to their effects on the bronchial muscles. Reported beneficial results from such inhalations in bronchopneumonia appear to me extremely doubtful. The claim that when thus administered epinephrin can check hemorrhage from the lungs also appears at least questionable. As for all such local applications only neutral or

feeble alkaline solutions may be employed (even weakly acid solutions being too irritant), it is well to remember that epinephrin rapidly deteriorates in alkaline solutions, and that consequently such solutions if not freshly prepared will have lost much or all of their epinephrin activity.

In the *alimentary canal,* suprarenal preparations may be applied directly to, and can exert their local vasoconstricting power only on, the esophagus, stomach, and lower bowel. In these situations, they have been employed with at least occasional success in treatment of hemorrhage resulting from carcinoma and ulcer, but the results are all too often unsatisfactory, as must be expected from the pathology. It should, however, be tried in these cases. Fifteen to thirty minims (1 to 2 c.cm.) of the 1 to 1,000 solution in 1 or 2 oz. of water may be swallowed without fear of harmful systemic effects. Hemorrhoids, whether bleeding or not, are occasionally benefited by introduction of epinephrin suppositories, or by small enemata of weak solutions (1-10,000 to 1-20,000), which may also prove useful in bleeding from the lower bowel. (While in a considerable number of cases I have given epinephrin solutions or suppositories rectally without obtaining any systemic effects, on one occasion a very violent systemic reaction followed the introduction of a suppository containing epinephrin. It is therefore possible that such effects may occasionally follow the use of epinephrin enemata.) Bleeding duodenal ulcers also would seem to be accessible to epinephrin administered by mouth or through a duodenal tube, but no mention of its successful use in such cases has been found in the literature. Before orally administered epinephrin can reach bleeding typhoid ulcers, it would appear certain that it must be rendered inert or be completely absorbed. Consequently, such use of this drug in typhoid hemorrhage seems useless. Its use hypodermically or intravenously to meet this indication will be discussed elsewhere.

In the *genito-urinary tract* the urethra, ureters and pelvis of the kidney are all accessible to the local application of epinephrin solutions, which have been employed with success in the treatment of hemorrhage and inflammation in these situations. From these mucous membranes there is little or no danger that there will be sufficient absorption to cause systemic effects, although Bastedo states that such have occasionally followed application to the urethra. Their use by oral and subcutaneous routes in treatment of renal conditions, and in the female genital organs, is discussed elsewhere.

In the *eye* instillation of epinephrin solutions ordinarily causes considerable smarting, but they may occasionally be used with benefit to facilitate the finding of a foreign body in cases where the conjunctiva is intensely hyperemic. (Cocain solutions would seem better, however, in such cases.) Local application of epinephrin appears to cause first a fall

and then a rise and later a fall of intra-ocular pressure. This rise might be harmful in a case of glaucoma.

Therapeutic Utilization of Remote (or Systemic) Vasoconstricting Effects.—When we come to consider the utilization of the remote (or systemic) vasoconstricting effects of suprarenal preparations, we enter a field where there is still much that is uncertain, and in which neither laboratory nor clinic has thus far supplied enough accurate knowledge to definitely settle many moot points. This is strikingly demonstrated by the diversity of opinion as to their value in the treatment of inaccessible hemorrhage.

Inaccessible Hemorrhage.—Although epinephrin (usually administered hypodermically) has been extensively employed in the treatment of *hemorrhage from the lungs,* there is still much divergence of opinion as to its value. This appears inevitable in view of the extreme uncertainty of prognosis in this condition, and our complete ignorance of the effects of such administration on the human pulmonary circulation. Laboratory investigation of intravenous administration shows different results in different animals and with varying dosage (Schäfer and Lim). Wiggers (*a*) (*d*) found that pulmonary hemorrhage was increased by epinephrin and advises against its use in hemoptysis. Bayer believes that the weight of opinion is against its use in these conditions, but there are many physicians who will strongly disagree with these conclusions. The power of suprarenal preparations to bring about increased coagulability of the blood may be cited as an argument for its possible value.

While having relatively little faith in its power to check pulmonary hemorrhage I still try it where other measures have failed. Relying more on a possible blood-coagulating effect than on any favorable action on the pulmonary vessels, I give it in small doses frequently repeated, 7 to 10 minims (0.5 to 0.7 c.cm.) of the 1-1,000 solution administered hypodermically every 20 to 30 minutes. Any pronounced objective reaction with increase in rate or force of heart beat is considered a contraindication to further trial. Of its value, I have been unable to form an opinion.

As to the efficacy of epinephrin in the treatment of *intestinal* and *renal hemorrhage* it is equally impossible to reach a definite conclusion. In animals, Wiggers (*b*), using small doses intramuscularly or intravenously, occasionally observed a checking of hemorrhage from the intestines, but obtained no results from the subcutaneous injection. He concluded that in intestinal hemorrhage which has not lowered blood-pressure other measures are of more value than epinephrin, but where a large hemorrhage has lowered the blood-pressure and is still continuing, he believes it should be given in gradually increasing dosage, the effect on the blood-pressure being closely observed. Just enough should be given to cause a moderate rise in the blood-pressure.

The doses employed may bring about relaxation of the gut at the site of a bleeding ulcer, which might well exert an unfavorable influence, but

on the other hand the blood-coagulating effect could be of decisive value. While for this indication epinephrin is ordinarily administered hypodermically or intravenously, various writers, among others Warren Coleman, report success from large doses administered orally (90 grains per diem of dried and powdered suprarenal substance). The clinical effect on intestinal hemorrhage of epinephrin injections remains problematical, but personally I am in favor of its cautious intravenous administration in cases of exsanguinating hemorrhage, and, in less severe cases, of its hypodermic administration in small doses, 10 minims every hour for several doses, followed by 6 to 8 doses at 3- to 6-hour intervals.

In *hemorrhage from the kidney* it has been administered hypodermically and orally with claimed benefit. In experimental renal hemorrhage Wiggers (*c*) found that the intramuscular or intravenous administration of moderate doses was very efficient. Those having faith in its value when orally administered, base their belief on the clinical outcome of cases in which it has been employed, and on the assumption that when thus administered it is to some extent excreted through the kidneys, and thus has the opportunity of causing renal vasoconstriction. That in the doses employed it produces such effects has not been demonstrated. The use of suprarenal preparations in the treatment of hemorrhage of the female genital tract is discussed elsewhere.

In internal hemorrhage of other causation, such as that of purpura hemorrhagica, yellow fever, and other diseases with a hemorrhagic tendency, its use orally or hypodermically is recommended, but its value in this type of case is, to say the least, very doubtful.

In various *affections of the skin* benefit has been claimed from the administration of suprarenal preparations. *Urticaria,* either chronic or acute, is often most promptly and strikingly benefited by their hypodermic administration (0.5-0.7 c.cm. 1-1,000 solution), although the relief obtained is frequently but temporary; and there are not lacking reports of cures (?) of chronic or recurring urticarias following regular oral administration. Good results are also claimed from the use of suprarenal preparations (orally or hypodermically) in *purpura hemorrhagica,* but such reports, together with successes from their use (internally or locally) in acne rosacea, and in various conditions associated with pigmentation must be viewed with considerable skepticism.

Therapeutic Utilization of the Antispastic Action.—Aside from the conditions in which the therapeutic effects of suprarenal medication would appear to be chiefly due to its vasoconstricting action, there are others in which it is employed for its antispastic action.

In *bronchial asthma* the clinical value of this type of pharmacodynamic action has been most brilliantly demonstrated. Bullowa and Kaplan in 1903 appear to have been the first to recommend the administration of epinephrin for the relief of asthmatic paroxysms. Although these authors

were led to its trial on the incorrect assumption that it would prove useful by causing constriction of the pulmonary vessels or by lessening the bronchial secretions, their experience and that of others quickly demonstrated that but few other remedies so promptly and satisfactorily relieve these distressing paroxysms. It was only in 1911 that Januschke and Pollak brought the correct explanation of its true method of action by their demonstration, that epinephrin prevents and relaxes spasm of the bronchial muscles. While the relief afforded persists in many cases for but a few hours, it is often much more lasting. Its freedom from the disagreeable and harmful effects of other drugs used for this indication has led to a very general conviction that we possess no other agent so useful here as is epinephrin. While occasionally success is obtained by oral or rectal administration,[43] in the large majority of cases the beneficial effects are to be obtained only by hypodermic administration. The dose ranges from 5 to 15 minims (occasionally 20 minims or more). Matthews reports success in a number of cases from its use as a nasal spray (1-4,000 to 1-10,000).

Not a few patients react very disagreeably to such injections. When this is the case, I have usually found that by trial a dose can be determined which is large enough to relieve the paroxysm without causing more than a mild systemic reaction, or none at all. The warning is often given against the use of this drug in asthmatics suffering from cardiac or arterial disease. As it has been repeatedly shown that the asthma is relieved without raising the blood-pressure (as a matter of fact, this is often found to have fallen when the paroxysm has been relieved), there seems to be little justification for this warning. While in many asthmatics epinephrin may be successfully used in repeated attacks, it is unfortunately true that (as a rule) if the paroxysms recur very frequently, the drug gradually loses its effect, and that even increased dosage no longer relieves. From time to time the claim has been made that, in addition to securing symptomatic relief, epinephrin, regularly administered, in some cases permanently cures bronchial asthma, but the experience of most clinicians does not bear out this claim.

The fact that epinephrin (in sufficient dosage) inhibits the movement of the *alimentary canal,* has suggested its trial in various conditions of hyperactivity, or spasm of stomach and intestines. Among these is the persistent vomiting of pregnancy, in which condition brilliant success has been frequently reported. Equally good results have been obtained in persistent vomiting of other causation. These results suggested to Maverick its trial in *seasickness,* in which condition he and others report many successes. Equally good results are claimed from oral

[43] In my personal experience in a relatively large series of cases satisfactory relief has been obtained only from hypodermic administration, although very rarely a moderate amount of relief has followed its oral administration. Of a limited number of cases in which the drug was given rectally, none responded at all.

and hypodermic administration. For oral administration, the dosage recommended is 4 to 6 mg. per diem. According to personal observations made on two transatlantic trips some years back, a proprietary remedy containing epinephrin did not prevent, relieve, or cure seasickness in a number of cases in which it was tried.

The antispastic action of epinephrin justifies its use in stenosis of the esophagus as recommended by Janowski.

The favorable effect of suprarenal medication on the diarrhea of Addison's disease, which has often been reported, may be due to this inhibitory effect. Eppinger and v. Noorden have also found that enemata (300 c.cm. of 1-150,000 adrenalin chlorid) are useful in the treatment of the diarrheas of Graves' disease. Yukawa's observation that oral administration of epinephrin increases the gastric secretion, suggesting its employment in achylia gastrica and hypochlorhydria has been confirmed by Loeper and Verpy, who also claim that in hypertonics it lessens spasm while in hypotonics it increases the frequency and intensity of gastric contraction.

Empiric Therapy with Suprarenal Substances

Suprarenal preparations have, like most other drugs, been used in the treatment of a large number of different conditions, in most of which they have proved of doubtful value or useless.

Their use in *various diseases of the bones,* however, cannot be dismissed so summarily. In *rickets* they have been tried by a number of clinicians, but the results have not been encouraging. In *osteomalacia,* a considerable number of observers report favorable results ranging from complete cure to marked improvement, while others report complete failure. At present no definite conclusion can be reached as to the efficiency of this treatment, but the results reported appear to justify its trial (Bossi (*a*) (*b*) (*c*), Novak, Cristofoletti). Bossi, the originator of this method of treatment, advises the hypodermic administration of 0.5 to 1.0 c.cm. of the 1-1,000 solution once or twice daily, every 10 or 12 days, stopping treatment for one or two days. Too early cessation of treatment has been followed by relapse in cases which had reacted favorably. Cristofoletti concludes that this method of treatment is more likely to prove successful in the osteomalacia of pregnant women than in other cases.

Epinephrin and the Arsenical Antisyphilitic Preparations.—In 1914 Milian reported that certain of the disagreeable effects following the administration of the arsenical antiluetics could be obviated by the use of epinephrin. In a more recent publication, he advocates as a routine measure the oral administration of 2 mg. (2 c.cm. 1-1,000 sol.) 1 hour before the injection of the salvarsan, repeating this 5 minutes before and 1

hour after the injection. In cases intolerant of salvarsan, he gives 1 mg. A.M. and P.M. by mouth for 4 days, and 5 minutes before the salvarsan is given he injects 1 mg. subcutaneously and 0.5 mg. intramuscularly. Beeson reports that 1 or 2 (!) [44] mg. given intramuscularly ten minutes before administration of the salvarsan proved beneficial in warding off unfavorable reactions.

Undesirable Results and Contraindications.—Mention has previously been made of some of the uncomfortable and at times alarming systemic reactions which follow the subcutaneous administration of ordinary doses of epinephrin. While very often in patients who have received ordinary-sized doses neither subjective nor objective phenomena are noted, it is by no means unusual for the following effects to occur: The patient experiences a feeling of general distress and anxiety, becomes pale and suffers from a sensation of precordial discomfort and pain, and shivers more or less violently. He may be conscious of an increase in the rate and force of the heart action, which may also become decidedly irregular and rarely he may suffer a more or less typical anginal attack. Occasionally the rise in blood-pressure may be very pronounced.[45] Vertigo, nausea, and vomiting, paresthesias, and heartburn are other symptoms which occasionally occur.[46] As a rule these exaggerated and more or less alarming effects last only a very few minutes and have no serious results. However, such pronounced effects on the blood pressure and heart action may well prove harmful in cases of hypertension, arteriosclerosis, apoplexy, aneurism, or feeble dilated heart. The sympathetico-mimetic action on the heart may in cases with premature (ectopic) contractions temporarily aggravate this condition, but Bayer's fear that it may be harmful in such cases seems justified only in connection with its use in chloroform narcosis. Arnstein and Schlesinger report that in elderly patients injections of ordinary doses are occasionally followed by a sharp rise followed by a sharp fall in the blood-pressure and by a tachycardia lasting several hours. They also state that in patients with coronary disease such injections may cause anginal attacks.

The local effects at the site of injection may also at times contribute to undesirable results. There is a growing belief among those frequently

[44] The intramuscular injection of 2 mg. of epinephrin may, in a susceptible individual, be followed by a very disagreeable systemic reaction. So large a dose should, in my opinion, never be given intramuscularly unless previous trial has shown that the patient is not sympathicotonic.

[45] I have seen a rise from 110 to over 22 mm. of Hg following an intramuscular injection of 1.5 cm. of adrenalin chlorid 1-1,000 solution (see p. 129).

[46] Such uncomfortable reactions ordinarily result only from unusually large doses or from the dose being accidentally introduced into a vein. Experience, however, has shown that they are especially likely to occur in cases of hyperthyroidism and other conditions associated with increased sympathetic tone (sympatheticotony). In cases where there is ground for suspecting such conditions epinephrin should be given in small doses (5 to 7 minims (0.3 to 0.5 c.cm.) of the 1-1,000 solution). My own practice is never to give more than 10 minims as the initial dose.

using local anesthesia that the prolonged vasoconstriction caused by the epinephrin, which is added to the anesthetic solutions, favors the development of local infection, and of necrosis (rarely). Consequently, there is a tendency to-day to lessen the concentration of the epinephrin solutions used. The arteriosclerosis produced experimentally justifies a fear that similar changes may occur in man. However, while this possibility cannot be denied, the weight of the evidence at present is against it.

The Thymus

While in the case of many of the endocrin glands employed therapeutically we have a fairly extensive knowledge of their physiological function, of their rôle in pathology and of their effects when administered, we have no such knowledge of the thymus. It is true that extirpation experiments of earlier investigators, such as Basch (*c*), Klose, Vogt, Matti (*a*) (*b*), Paton (*a*) (*b*) and others, indicated that this gland exerted an important influence on growth, especially of the bones, and that there was an important relationship between the thymus and the thyroid, the testicles, and perhaps still other endocrin organs. Later investigations, however, such as those of Pappenheimer (*a*) (*b*), Park, Nordmann (*a*), Morgulis, Gies, Uhlenhuth and others have failed to corroborate these conclusions. We must therefore admit that, as recently pointed out by Hoskins (*b*) and Uhlenhuth (*f*), there are no facts known which warrant the claim that the thymus does or does not produce any internal secretion which is required to maintain the normal physiological condition of the organ.[47] When orally administered, thymus preparations exert no immediate pharmacodynamic actions, and, although the intravenous injection of extracts of the gland causes a striking fall in the blood-pressure, there is nothing specific in this action as it is similar to that exerted by extracts of various other organs. (Basch considers it due to coagulation phenomena.) The organotherapeutic employment of this gland must therefore, for the time being, rest not at all on any rational or theoretical foundation but entirely on an empiric one.

Thymus medication has been employed with reported benefit in a large number of diseases of various types. The literature shows that it has been considered useful or curative in goiter (both simple and toxic), myxedema and cretinism, infantilism, marasmus, acromegaly, Addison's disease, rickets, chlorosis, chorea, epilepsy, dementia præcox, gout, chronic arthritis, arteriosclerosis, carcinoma, tuberculosis, and hemorrhoids (!), and doubtless a more thorough search would enlarge this list. An analysis of the reported results of thymus therapy in the above mentioned diseases

[47] Uhlenhuth believes, however, that the thymus does produce an internal secretion, but one which, as far as we know at present, exerts only a toxic effect and which he believes is probably the substance which causes tetany.

would appear to justify the conclusion that in some of them administration of thymus appears to be occasionally of benefit, that in others it is of doubtful value, while in still others there is no real evidence that it is of any value at all.

Exophthalmic Goiter.—In 1893 Owen reported marked improvement in a case of Graves' disease, following the administration (through mistake of a butcher) of thymus gland in place of thyroid. As he found that cessation of thymus medication was followed by relapse and its resumption by renewed improvement, Owen naturally concluded that the thymus therapy was responsible for the improvement noted. Following Owen's publication a number of clinicians, among others Von Mikulicz, reported beneficial results following thymus feeding in patients with exophthalmic goiter and also in those with *simple goiter.* While, as is usually the case with new methods of treatment, the early reports were those of practically uniform success, more extensive experience soon showed that this enthusiasm was not justified by the facts, and that in the majority of cases of this disease thymus feeding is followed by little, if any, benefit. Of late it would appear that this treatment has been used less frequently, perhaps, than it should be, in view of the undoubted improvement which, according to many capable clinicians, has followed its administration. Kocher (*b*), in a recent publication, states that in his own experience thymus feeding was followed in one-half of the cases in which it was tried by improvement, which was never very striking, and that, even in doses of 100 grams daily, it caused no bad effects. He states, however, that it was not well borne in three cases. He prefers to use Poehl's Thymin, of which he usually gives 2 to 6 tablets (0.5 gm.) daily for three to six weeks, starting with the smaller dose and increasing gradually. Bram, in his recent book, quotes varying opinions as to its value.

In view of the present divergence of opinion as to the exact nature of the perversion of function in Graves' disease and of the uncertainty as to the physiological significance of the thymus and its internal secretion, the clinical results of thymus therapy furnish the sole criterion for an estimate of its value in this disease. These results appear to be in some cases at least of sufficient value to justify its trial in cases not responding satisfactorily to other treatment.[48]

If thymus feeding is actually beneficial in exophthalmic goiter it would seem almost certain that it cannot exert any favorable influence in cases of *myxedema* and *cretinism,* and yet Basch (*c*) is able to cite authors reporting favorable results in these conditions of hypothyroidism.

[48] Arguments from a theoretical standpoint against the possibility that thymus administration can exert a favorable influence in Graves' disease are the fact that the thymus is often much enlarged in severe cases, the claim of Capelle and Bayer (who believe that an internal secretion of the thymus aggravates the symptoms of this disease, especially the tachycardia) that they have seen improvement following thymectomy, and Bircher's claim that in animals implantation of thymus causes symptoms of Graves' disease such as tachycardia and tremor.

The reputed influence of the thymus on bone development led Mendel to administer it in rickets with reported benefit, but his claims have not been substantiated.

In *arthritis deformans* (metabolic osteo-arthritis) Nathan (*a*) (*b*) reported beneficial results from prolonged thymus feeding. As a result of his experience with 186 cases he stated that: "When the thymus is conscientiously taken for a long time and the patient is otherwise judiciously handled, marked improvement, if not a perfect cure, can always be expected." His views have not been generally accepted and my own limited experience with this method of treatment and careful reading of his reports lead me to agree with Carlson (*a*) that "the otherwise judicious handling" was the more important cause of the results reported. In his series Nathan used thymus in doses of two to four five-grain tablets thrice daily for long periods.

In *chorea* Haneborg reports benefit from thymus three to six tablets (size not stated) daily (in rheumatic cases combined with salicylates). He also reports that he and others have found it useful in *epilepsy*. His communication, available only in the form of an abstract, does not carry conviction. Of Gwyer's report of beneficial results from thymus therapy in arteriosclerosis, hemorrhoids (!), cystic tumor of the breast, pulmonary tuberculosis, and cancer it may be said that it is such reports as this which do much to discredit organotherapy. Ludlum and Corson-White report that three out of six cases of *dementia præcox* (which were considered by them to be cases of hypothymism) were cured by thymus feeding (no dosage or other details of treatment given). The three cases which were not cured were very advanced cases of long standing.

Testicle

The therapeutic employment of testicular products is of historical interest, in that it was almost the only animal product prescribed in ancient times to which any therapeutic powers can be prescribed, and also because modern organotherapy dates from Brown-Séquard's (*b*) report in 1889 of the results of his administration to himself of a testicular extract. Although, up to the present time, the great majority of authorities have failed to accept most of the claims made by him and his followers as to the therapeutic efficiency of testicular products, the historical interest attached to his reports justifies at least a brief notice of his views. In his first communication he reported that, as a result of the injection of an extract prepared from dogs' testicles, he, a man of 72 years, immediately experienced a remarkable increase of strength and endurance and of his mental efficiency, as well as an equally striking improvement in the functions of micturition and defecation. Four years later, with d'Ar-

sonval, Brown-Séquard, as the result of their own observations and the reports of over one thousand physicians, expressed certain conclusions, which may be summarized as follows: Although testicular extract does not possess any direct curative influence, it may, when injected hypodermically, cure or ameliorate diseases, organic or functional, of the most varied character, or at least cause their effects to disappear. These effects were attributed by them to two types of action: one, a beneficial action on the nervous system, which reacts favorably on the diseased parts or their functions, the other, depending on the introduction of new material into the blood, bringing about the formation of new cells or other new anatomical material.

Following the publication of Brown-Séquard's claims, there ensued an epoch in which testicular therapy was employed most extensively and extremely irrationally. Both from clinic and laboratory emanated reports ascribing to testicular extracts most marvelous powers of which at the present time relatively little is accepted.

After excluding many more or less unfounded conclusions, we may consider that the laboratory evidence is conclusive that the testicle contains an internal secretion, which is contained in properly prepared extracts, and which, when administered to a proper subject, can exert a specific effect on the sexual characteristics in certain animals, and by inference probably in others. Evidence of this has been furnished by the observation that the administration of testicular extracts to female chickens and pigeons caused the development of male characteristics, and by the effect of testicular extract on the development of castrated frogs. Zoth (*a*) (b) and Pregl have demonstrated another very remarkable effect resulting from the injection of testicular extract. These investigators found that while such injections given daily for one week or daily exercise for the same period brought about no material increase of muscular power, the combination of the daily injections and the daily exercise resulted in a striking augmentation, amounting to as much as 50 per cent of the initial value.

If one were able to accept all or nearly all of the claims, which have been made by various clinicians for the curative powers of testicular extracts, we would be forced to the conclusion that in it had been found the long sought panacea.

A large number of these preposterous claims centered in Poehl's spermin,[49] which was considered by its discoverer to be one of the normal protective agents of the body. Brown-Séquard laid great stress on the possession by testicular extract of general tonic powers, and Poehl made a similar claim for spermin, this being due, in his opinion, to its being a powerful positive catalytic agent, i. e., an accelerator of oxidation. It

[49] This substance (or mixture of substances) was prepared by Poehl from a number of organs but, according to him, is present in largest amount in the testicle.

was to the possession of this property that the claimed therapeutic effects of spermin in so large a variety of diseases was attributed by Poehl, who was a disciple of the school which saw in autointoxication the main feature of many diseases.

The exaggerated claims so generally made as to the value of testicular therapy have brought it into disrepute, so that in recent literature there are to be found but few reports of its employment, but from conversation with physicians and reports from druggists it is evident that testicular preparations, usually in combination with other products, are still frequently prescribed. Of the more recent reports of favorable results from its employment those of Bloch and Sharff appear worthy of notice, as they are fairly typical in the claims made and also in the unsatisfactory character of the clinical data. Bloch (*a*) (*b*) (*c*) has made use of testogan, a preparation by the use of which he has sought to combine the prompt aphrodisiac action of yohimbin with the slower "central erotizing" action of testicular extract. In cases of his own and those reported to him by a number of others, he has reported such results as follows: In a 36-year-old officer with bisexual characteristics and sexual perversion, forty injections of 1.0 c.cm. each and 80 tablets restored libido and potentia and caused the crines to become of a masculine type; 80 capsules caused a metamorphosis of a youth of 15 years with undeveloped genitalia and feminine attributes; in all but eleven of fifty cases of impotence (apparently functional or psychic), oral or subcutaneous administration, or a combination of the two, brought about a partial or complete return of libido and potentia; restoration of potentia even when the result of loss or atrophy of the testicles; great improvement in cases suffering from sexual neuroses or neurasthenia. From injections of testiculin,[50] Sharff obtained no results of any moment in one prostatic case, and subjective improvement of prostatic symptoms and improvement in strength in another. In several neurasthenics with sexual features he found it beneficial. (One of these was a woman!) He concluded that it was an "excellent tonic and analepticum," but the clinical data presented by him are not such as to compel acceptance of his claims. Ludlum and Corson-White, who believed that the testicle is antagonistic to the pituitary, have reported that injection of Brown-Séquard's fluid was followed by cure in four insane patients, who presented signs of hyperpituitarism, but with so little detail that the report is almost (if not quite) without value.

From consideration of the available data I am of the opinion that the evidence that testicular products are of therapeutic value is at best merely suggestive. However, Zoth and Pregl's observations on their effect on development of muscular power in man, and the demonstration by various observers of their influence on development of secondary sexual characteristics in animals furnish a basis for the hope that eventually it will be

[50] From the firm of Freund und Redlick.

shown that such products can exert a more or less specific and beneficial effect in human beings.

In contrast to the doubtful or negative results of the administration of testicular substance are the undoubted effects resulting from *transplantation* of these glands. Although long ago the experimental proof was brought that such grafts could survive and, at least for a time, supply the necessary amount of their internal secretion, the first operation of this nature on a human being was that performed in 1912 by Hammond and Sutton, who for cosmetic purposes grafted a testicle, removed from another subject, onto the atrophied testicle of their patient. Since that time testicular transplantation has been performed a number of times by different surgeons, notably by Lydston (*a*) (*b*) (*c*), for therapeutic indications. The operation would appear to have, in many instances, produced results on the sexual function and the general state of the patients, which can be explained only on the assumption that the grafts have, for periods ranging from a few months to several years, supplied a certain amount of internal secretion. Among those reporting successes in this relatively new field[51] are Lydston, Morris, Lespinasse, Stanley and Lichtenstern (*a*) (*b*). While this therapeutic procedure is still in the stage when the definite limits of its indications and utility have not yet been established, the results reported thus far are most suggestive. It would seem that among the many victims of the great war there must be many who are fit and willing subjects for the further testing of the merits of this procedure.

Ovarian Substances

These are treated of in their therapeutic aspects elsewhere in these volumes.

Placenta

Basch's conclusion that the preparation of the breasts for lactation and the inauguration of this function are both due to a substance or substances formed or contained in the placenta, having been experimentally corroborated by several other investigators, there appears to be some ground for considering the placenta an organ of internal secretion and for the administration of placental extract as a lactagog.

A number of observers have reported favorable results from the oral administration of such preparations to nursing mothers with a scanty milk supply, but the evidence presented of its clinical value is not at all convincing.

In 1913 Miklas, after reviewing the experimental and clinical evidence

[51] In the available medical literature I have found no other reference than that in Voncken's article to Voronoff's work, which has been so exploited in the lay press.

(including 5 cases of his own), reached the conclusion that oral administration of placental substance slightly increased the amount secreted by nursing women, whose supply was already ample, but that its efficiency had not yet been shown where the milk supply was scanty. McNeile, from observations conducted for eleven days on 8 patients and their babies and on 8 controls, felt that he could draw no definite conclusions as to the value of placental feedings, but appears to have some confidence in it. Cornell, from observations on 100 cases, who received dried placental substance, 5 grains t.i.d. for 12 doses, and 70 controls, concluded that placental therapy exerted a favorable effect on the production of milk, basing this conclusion on the earlier gain in weight in the babies of the placenta series.

As the evidence presented in these three papers, while suggestive, is by no means convincing, it would appear that the therapeutic value of administration of placental substance is still very questionable.

Mammary Gland

Although it is still doubtful whether or not the mammary gland produces an internal secretion, extracts made from it have been used with claimed benefit in various conditions. Feodoroff, Goldmann, Luncz, Osborne (*a*) and others, report a beneficial effect on uterine hemorrhage. Bell, Feodoroff, Mekerttschiantz (*a*), and a number of others, are convinced that the administration of mammary substance brings about a remarkable diminution in the size of uterine fibroids. Mackenzie has claimed that it is a true lactagog, but the observations of Gavin and Gaines speak strongly against this view.

The majority of the gynecologists of the present day do not appear to accept any of the claims which have been made for the efficiency of mammary therapy. It is noteworthy that recent literature contains very few references to its employment.

Pancreas

Although the pancreas undoubtedly possesses at least one internal secretion of great importance, no one has yet succeeded either in laboratory or clinic in obtaining by administration of pancreatic preparations any effect whatever which could be attributed to the action of its internal secretion. Various claims[52] to the contrary notwithstanding, there is up to the present time no true organotherapy of the pancreas. The only

[52] Such claims have been made by Rennie and Fraser, Walko, Combe, Cowles, Zuelzer, Crofton, Harrower (*a*) and others, but there can be no question that these authors have merely deceived themselves and others.

therapeutic applications of the pancreas rest on the utilization of the proteolytic, glycolytic, and lipolytic ferments which are present in its external secretion, the pancreatic juice.

On the surface it would appear a relatively simple matter to utilize these properties of the pancreas in the treatment of the disturbances of digestion and absorption which result from diminution of or entire absence of these ferments in the intestine. In practice, however, such application is rendered difficult, in the first instance, by the fact that the gastric juice acts destructively on the pancreatic ferments [53] and, in the second place, by the fact that even very large amounts of pancreatic preparations, which may be brought into the duodenum without having been destroyed by the gastric juice,[54] do not bring about as complete a digestion and absorption of the food ingested as occurs under the influence of normally secreted pancreatic juice.

The effect of administration of various pancreas preparations on the digestion of proteids and fats has been very thoroughly investigated, both in animals and in human subjects, in whom, as a result of pancreatic disease or obstruction of the pancreatic duct, the entrance of the pancreatic juice into the duodenum has been completely or entirely prevented. While there are some discrepancies in the findings of the different investigators, they have with few or no exceptions been able to demonstrate that the administration to such cases of very large amounts of pancreatic products brings about a more or less marked increase, especially of the proteid absorption and, to a less extent, of the absorption of fat.

In Ehrmann's case of chronic pancreatitis the ingestion of 25 grams of pancreatin per diem was followed by an increase of the nitrogen absorption from 57 per cent to 83 per cent of the nitrogen intake, but the microscopic examination of the feces showed there was still very incomplete digestion of the meat fibers; in two such cases, Gros observed no effects from the daily ingestion of 5 grams of Pankreon, but from twice that amount obtained a rise of the nitrogen absorption from 50 per cent and 40 per cent to 88 per cent and 70 per cent, but very little improvement in the absorption of the fat. In these two cases fresh pancreas also increased the nitrogen absorption markedly but did not alter that of the fat. Glässner and Sigel obtained better results when large amounts (30 grams) of soda were given with pancreatin. Tauber, in seven cases of icterus and cirrhosis of the liver, obtained practically no effects from one gram of pankreon three times daily. In Tileston's case of chronic pancreatitis with diabetes, cirrhosis of the liver, and achylia, the administration of pancreatin caused an improvement in the absorption of both nitrogen and fat.

[53] The lipolytic ferment is only slightly impaired by the gastric juice.

[54] This can be accomplished by administering sufficient alkali to keep the stomach contents neutral.

The above cited and numerous other similar observations definitely prove that the ingestion of sufficiently large amounts of fresh pancreas or of any good [55] pancreatic preparations will to a very considerable extent increase the digestion and absorption of proteid and (but to a less extent) of fat. In cases with normal HCl secretion, it would appear advisable to lessen the acidity of the stomach contents by administering large doses of soda just before or at the same time with the pancreatic extract. Quite possibly better results might be obtained by introducing a suspension of pancreatin through the duodenal tube.

Addendum

Borchardt, L. ("Erhöhung des Agglutininspiegels durch Organpräparate als Ausdruck leistungsteigernder Wirkunken in der Organotherapie." *Therap. Halbmonatsh.*, Berlin, 1920, xxxiv, 536-541) claims that the administration of thyreoidin (8 tablets on two consecutive days) brings about a marvelous increase in the rapidity with which and extent to which typhoid vaccines increase the agglutinative powers of the blood. He also claims similar effects from the hypodermic administration of one dose of certain other endocrin preparations—e. g., adrenalin, hypophysin (or a combination of the two), and spermin.

In his article on Organotherapie (*Ergebn. d. Inn. Med.*, Berlin, 1920, xviii, p. 293) he quotes Rosenthal as confirming his results. The far-reaching significance both for theory and practice of these claims is apparent.

[55] Test tube examination of commercial preparations has shown that they are often inert or nearly so.

Ovarian Therapy . . . . . *Emil Novak*

Introduction—Preparations Available for Ovarian Therapy—Extract of the Entire Ovary—Corpus Luteum Extract—Soluble Extract of Corpus Luteum—Ovarian Residue—Physiologic Action of Ovarian Extract—Conditions Indicating Ovarian Therapy.

Ovarian Therapy

EMIL NOVAK

BALTIMORE

Introduction

Gynecologists have played a leading part in the development of organotherapy, and the use of ovarian extracts of one form or another has become an important part of every up-to-date gynecologist's armamentarium. Originally introduced at the Landau clinic in Berlin in 1896, this form of organotherapy has achieved a wide field of usefulness. This is true in spite of the fact that we are still ignorant of the active principle, or principles, of the ovaries, and, for that matter, of many points relating to their physiology.

Preparations Available for Ovarian Therapy

Various forms of ovarian extract are available for administration. It is unfortunate that there has been no effort at standardization of these products, each manufacturing house independently putting out its own preparations, with their prescribed doses. As Morley (*a*) (*b*) says, "Ovarian extract in the reports of various investigators may mean any one of various things—an aqueous, alcoholic or ethereal extract, or even perhaps the desiccated gland in powder form." It is difficult to speak of dosage unless the various preparations of each manufacturer are specified by name, which would scarcely be in good taste. Furthermore, literature on each preparation is easily procurable from the various manufacturing houses.

Extract of the Entire Ovary.—This substance is most frequently employed in the form of tablets representing usually about five grains of fresh ovarian substance, derived from the ovaries of the cow or sow. The extract is also, however, available in powder form, or in the form of capsules, or of a soluble extract, suitable for hypodermic medication. Among the early workers with ovarian extract was Iscovesco who, on the basis of his work on the lipoids of various animal extracts, was able to develop a technic of preparation without the destruction or loss of the active principle. A somewhat similar technic was later described by

Herrmann, who believed that he was thus able to isolate the active principle of the ovary.

Corpus Luteum Extract.—This is procurable commercially in the form of powder, capsules, tablets or aqueous solution. There has been much discussion as to whether the extract should be obtained from the ovaries of pregnant or of non-pregnant animals. It is difficult to decide this question in the present state of our knowledge. Certainly the corpus luteum reaches its fullest development during early pregnancy. On the other hand, during pregnancy, menstruation is absent, suggesting that perhaps the menstruation-producing hormone of the corpus luteum is at this time held in abeyance. Osborne (*b*) does not believe that there is any great difference between the effects of the extracts prepared from pregnant and non-pregnant animals. Seitz, Wintz and Fingerhut have shown, in the case of beef ovaries, that the hormone activity of the corpus luteum differs at different stages. They have isolated two separate substances whose action is quite antagonistic, and each of which predominates at different stages of the corpus luteum. One of these they call lipamin, which is said to exert a stimulating effect on the growth of both the internal and external generative organs. It is the predominant secretion in the early corpus luteum, and its subcutaneous injection is said to bring on the menstrual flow, in the case of amenorrheic women. The other substance, luteolipoid, predominates in the later stages of the corpus luteum, and exerts an inhibiting effect on the menstrual period. These two substances have been prepared in tablet form in Germany, but, so far as I know, not in this country. The question of the variations in the hormone activity of the corpus luteum at its different phases is of obvious importance from the standpoint of ovarian therapy, but comparatively little of a definite nature is as yet known on this point.

Soluble Extract of Corpus Luteum.—This substance is worthy of special mention because, within recent years, many clinicians have been administering corpus luteum extract hypodermically in soluble form. The substance is now conveniently prepared in ampoule form (1 c.c.), representing 20 mg. of the corpus luteum substance. For most indications it is administered in doses of one ampoule every second or third day, but it has been used much more frequently—by some every day, or even twice a day. The advantages of this form of administration are those which pertain to hypodermic medication generally. It is precise, it enables the physician to keep the patient under direct personal control, it avoids the disagreeable digestive symptoms often associated with the oral method, and it carries with it a psychic element which is lacking in medication by the mouth. Hirst (*a*) urges that the extract be injected deeply into the muscles, preferably into the deltoid, claiming that it is too irritating for injection into the subcutaneous tissue. Dannreuther speaks enthusiastically of the results of this form of ovarian therapy, stating that such

subjective symptoms as vertigo and nausea, so often complained of by patients taking desiccated gland by mouth, are seldom noted following injections of the soluble extract. He looks upon headache as the chief manifestation of overdosing by the soluble extract. The results are more rapid than by the ingestion method, which may be resorted to once improvement is begun by the injection method.

Ovarian Residue.—Recently Graves (*a*) (*b*) has suggested the use of a substance representing the residue of the ovary after removal of the corpora lutea. The basis of this is his belief that the chief source of the internal secretion of the ovary is in the interstitial cells. He believes that the results of treatment of various conditions by this ovarian residue are superior to those obtained from the use of whole ovary or of corpus luteum alone. Tyler has reported good results from this form of therapy, as has also Clagett. It is as yet too soon, however, to decide whether the use of this substance will yield results which are better than, or perhaps as good as, the older methods of medication. Ovarian residue, it may be added, is obtainable not only in solid form but also in solution in the form of ampoules.

Physiologic Action of Ovarian Extract

Comparatively little work of a really scientific nature has been done on the physiologic effects of the various ovarian extracts which are used so generally—at times promiscuously—by clinicians. A number of interesting studies of this sort, however, are to be found in the recent literature. One of the earliest is that of Federoff, in 1899, who concluded that the most important effect was a slowing of the heart beat and an elevation of the blood pressure. Concerning this last point there has been a great deal of discussion. The most complete recent study has been by Goñalons. This investigator insists that, in order to obtain accurate observations, the solutions must be used within a very short time after preparation. He finds that "immediately following the injection of 20 c.c. of maceration or decoction of gravid corpus luteum, there is a rapid hypotension of 50, 60, or even 80 mm. of mercury. The pressure falls rather rapidly, cardiac pulsations are generally considerably weakened, and there are sometimes in the first moments deep convulsive respirations. After 1, 2 or 3 minutes the pulsations strengthen and the pressure rises. This is relatively rapid at first. After 5, 7 or 10 minutes, sometimes more, the pressure returns to normal; at other times it persists a little diminished." The results from a maceration or decoction of the ovary are somewhat similar, though usually less marked than with gravid corpus luteum. Solutions of either gravid ovary or gravid corpus luteum produce at first a lessening in the amplitude of the heart beats, which is generally accompanied by a tachy-

cardia. Especially interesting is Goñalons' observation on the effect of ovarian and pregnant corpus luteum on the uterine muscles. He finds that both produce a tonic contraction with an increase of the rhythmic contractions.

These results are, in the main, similar to those obtained by Barry. They differ, however, from those of Fuchs, Stickel, and Bell and Hick. The first named author describes a depressant action. Stickel observed no effect at all from the intravenous injection of ovarian extract, while Bell and Hick saw no results from ovarian extracts in the virgin uterus, but a stimulation in the case of the pregnant organ. Stimulation of the uterus was also observed by Ott and Scott, and also by Itagaki.

In a recent series of 110 experiments on the effect of extracts of the ovary and corpus luteum on the excised uteri of the rat, guinea-pig, pig, dog and cat, and also a number of experiments on the Fallopian tubes of the pig, Matsumoto and Macht found that "in all cases both ovarian and corpus luteum extracts produced a powerful stimulation of the contractions and an increase in the tonus of the uteri. It was also found that in all cases the excised uterus preparations reacted more quickly and to smaller doses of corpus luteum extracts than to extracts of the ovarian substance." The same observation was also made on the musculature of the Fallopian tube. The authors emphasize, however, that these effects are not to be looked upon as specific, for stimulation of the uterus was produced by practically every gland or organ with which they experimented.

Matsumoto and Macht found that the freshly excised vas deferens of the rat was the preparation most sensitive for testing the corpus luteum. The degree of contraction was found to vary directly with the doses administered. This reaction seems to be specific for the corpus luteum, not being evoked by ovarian substance. The authors therefore suggest that the vas deferens test may be considered useful as a means of assaying corpus luteum preparations.

Goñalons, from observations upon nursing women, believes that the administration of the corpus luteum of the pregnant cow exerts a pronounced galactogogue effect. These observations, he maintains, are demonstrable also by experiments which he reports upon lactating cats. Ott and Scott also found that hypodermic injections of corpus luteum caused the mammary glands of rabbits to hypertrophy to twice the normal size, with the appearance of milk.

Finally, reference may be made to the effect of ovarian and corpus luteum extracts on the pupil of the eye, as determined by Macht and Matsumoto. The ovarian extract was found to produce little or no effect, but the corpus luteum extract, in the form of either the fresh gland or the desiccated product, produces dilatation of the pupil in from 30 to 60 minutes, according to the strength of the preparation used.

Conditions Indicating Ovarian Therapy

Ovarian Therapy in Amenorrhea, for Menopausal Symptoms and for Functional Uterine Hemorrhage

These topics are treated in the chapter on Clinical Syndromes of the Female Gonads.

Ovarian Therapy for Obesity of Hypogenital Origin.—Obesity is a frequent manifestation of hypogenitalism, either the physiological hypogenitalism of the menopause or the acquired form due to disease or to the surgical removal of the ovaries, as discussed in the chapter on Ovarian Clinical Syndromes. The indication for ovarian therapy in these cases would seem quite clear, although it is only fair to say that the administration of any of the ovarian or corpus luteum preparations alone usually does not yield very striking results. Polytherapy in the form of mixed ovarian and thyroid treatment is far more satisfactory. The thyroid extract in these cases is given usually in small doses, especially since its use must be kept up for a long period of time.

It is rarely necessary to give more than about three grains a day, and often the amount will be much smaller. This mixed treatment frequently gives excellent results, not only in the reduction of obesity, but also in the amelioration of the disagreeable subjective symptoms so commonly associated with hypogenitalism.

Ovarian Therapy in Nausea and Vomiting of Pregnancy.—In 1916 Hirst (*b*) suggested the hypodermic administration of soluble corpus luteum extract for the vomiting of pregnancy. According to his view "it is not unreasonable to suppose that there is sufficient absorption from the corpus luteum of pregnancy to account for disappearance of nausea, especially when one realizes that the nausea begins to diminish at the time the corpus luteum has reached its acme of development." With this idea he gave 1 c.c. of the extract (20 mg.) daily, and reported 80 per cent of successes in the 5 cases in which it had been used. In all of these the injection was given into the muscles. In a second paper (1921) he (*c*) urges that the injection be given into the veins. The advantages of this method he summarizes as follows: "1. The material used is carried directly into the circulation, giving the most rapid absorption possible. 2. It is possible and advisable to use a considerably larger dose (two or three ampoules) than is possible with the intramuscular injection, in which more than 1 c.c. causes considerable local reaction. 3. Each ampoule contains only 0.2 gm. of the extract, and in this way the necessary total quantity can be introduced more easily and quickly. 4. There is no local reaction or discomfort of any kind after the injection. 5. Intravenous administration

often controls the vomiting promptly, in cases in which intramuscular use has failed."

The dosage of the corpus luteum extract for the control of the nausea of pregnancy varies with the severity of the case. In the milder cases Hirst advises giving 2 c.c. daily, and in the pernicious cases the same amount may be given even twice daily. With these amounts unpleasant reactions are said not to occur.

On the whole, it must be evident that there is no real scientific basis for the form of treatment recommended by Hirst. I am frank to say that the results in my hands have not been as brilliant as those which Hirst reports. Rongy and others likewise have reported disappointing results from this method, and it remains to be seen whether it will ultimately achieve a place for itself in the treatment of the nausea of pregnancy.

Ovarian Therapy in Neurological Practice.—Climenko has reported good results from the use of corpus luteum extract in the treatment of various mental disorders. He mentions especially a case of "menstruation insanity" of the type described by Kraft-Ebing and a case of mild manic-depressive insanity. The results in a patient with hysteria, associated with "mechanical obstruction" of the uterus, were questionable. Several other cases are cited as illustrating the possible value of corpus luteum extract in the treatment of female neurological and psychiatric practice, but on the whole the evidence brought forth is rather unimpressive. The same statement may be made as to the treatment of epilepsy by ovarian extracts. Cases have been reported in which good results are said to have been observed, as in the three patients treated by Ashe, but the empiricism of such medication is obvious, and its results are probably of no great value.

Ovarian Therapy in Climacteric Hypertension.—Hopkins has recently reported a series of fifty-one cases of hypertension occurring in women at the time of, or just after, the menopause. He presents evidence which he believes indicates that these cases are unlike the ordinary cases of high blood pressure in men at the corresponding age, and explains them as due to the withdrawal "of at least a part of the secretion of the ovary" at the menopause. He suggests the designation of "endocrinal hypertension" for these cases, which he looks upon as of relatively benign type. In addition to the general régime customary in hypertension cases, he advocates the giving of corpus luteum, especially by the hypodermic method.

Ovarian Therapy in Sterility and Dysmenorrhea.—Ovarian and corpus luteum extracts have been used in the treatment of sterility, though with rather indifferent results. Fallenberg advocates large doses of the extracts, beginning with five grains a day and gradually increasing until at the end of a month 30 grains a day is being taken. The treatment should be continued for one year. Solomons believes that the most suc-

cessful cases are those in which menstruation is scanty. Certainly there would seem to be good reason for organotherapy in those cases of sterility associated with congenital hypoplasia of the uterus, and often accompanied by dysmenorrhea or amenorrhea. Here the ovarian extract is best combined with extract of anterior pituitary lobe. Rational though such medication may be, the clinical results are rarely striking and often quite negligible.

What has been said concerning the treatment of sterility would apply with equal force to the treatment of dysmenorrhea. It need scarcely be said that secondary dysmenorrhea, i. e., the form due to the presence of definite pathologic conditions in the pelvis (inflammatory disease, neoplasm, displacements, etc.), offers no field for the use of ovarian therapy. In primary dysmenorrhea, however, we have to deal with a developmental defect—a uterine hypoplasia—which is assuredly of endocrine origin. Dysmenorrhea and sterility are commonly associated in this condition. The indication for organotherapy is a real one. Extracts of the entire ovary are here indicated, in combination with anterior pituitary substance and often with thyroid.

The Relations Between the Endocrin Organs and the Autonomic Nervous System . . . . . *Francis M. Pottenger*

Introduction—The Suprarenal Glands—The Thyroid Gland—The Hypophysis—The Pancreas—The Gonads—The Parathyroids—The Thymus.

The Relations between the Endocrin Organs and the Autonomic Nervous System

FRANCIS M. POTTENGER

MONROVIA

Introduction

Hormone Control of Bodily Functions.—The close relationship which exists between the glands of internal secretion and the vegetative nervous system may be inferred from their developmental history. Primitive forms of life are without nervous systems, and whatever response to stimuli and whatever correlation of action takes place in them does so through chemical action. Later in the stage of evolution, as the organism becomes more complex, a more accurate and more rapid coördination is required. For this, in addition to the chemical control, a nervous system is developed. In the higher forms of life, then, we have this double reciprocal control of all involuntary or vegetative functions. Stimulation of the glands of internal secretion takes place through the vegetative nerves, and the hormones produced by the glands in turn stimulate vegetative nerve structures. Langdon Brown (1920), in discussing the relationship between the adrenals, thyroid, and pituitary on the one hand and the sympathetic nervous system on the other, says: "This association is reciprocal—as not only does the sympathetic nervous system stimulate the secretion of these ductless glands, but their secretion increases in turn the sympathetic response. Thus, the sympathetic nervous system, the endocrin glands, and the gonads form a basic tripod, entrusted with the duty both of the preservation of the individual and the continuity of the species. Their relationship is shown in disease as well as in health, and is reflected in many of the neuroses and psychoses."

Extensive Scope of Endocrin and Autonomic Influences.—The importance of these two subjects can be fully appreciated only when the fact is grasped that every normal action expressed in the unstriated musculature of the body, the heart, and the secreting glands, must be brought about in response to stimulation by the chemical substances secreted by the glands of internal secretion or by the vegetative nerves. There cannot be a

single sensory or psychical impression which does not, at least theoretically, affect the vegetative nerves and endocrin glands. Further, if the impressions are strong, they upset the equilibrium in the endocrin and vegetative systems and produce symptoms of disease. Many symptoms which manifest themselves in the so-called vegetative structures (smooth musculature, heart, and secreting glands) are due to disturbances in the normal physiologic equilibrium of these two systems.

Not only are both the endocrin and vegetative systems subject to impulses of a physical nature, but each system is influenced by psychical impulses and by impulses which originate in the other system. It is now our purpose to inquire into this relationship and show, as far as we are able, how the vegetative nerves influence the endocrin glands and how the chemical substances produced by these glands influence the visceral nerves.

Morphology of the Autonomic Nervous System.—The autonomic or vegetative nervous system, as illustrated in Plate I, consists of two divisions, the sympathetic and parasympathetic. The sympathetic division of the vegetative nervous system is sometimes called the thoracicolumbar outflow, because it takes its origin in the cord from the thoracic and upper lumbar segments. The parasympathetic division, on the other hand, is called the craniosacral outflow, because the nerves composing it arise from the brain and the sacral portion of the spinal cord. Thus, the vegetative fibers in the third nerve arise in the midbrain, those in the seventh, ninth, and tenth in the bulb, and the pelvic nerve in the sacral segments of the cord. The parasympathetic division is also sometimes called the "autonomic" or "vagus system"; but the use of the term parasympathetic is preferable, because autonomic is also applied to the entire vegetative system, hence the use of it as applied to one division leads to confusion. Another source of confusion, particularly in the earlier literature, is the use of the term "sympathetic" as synonomous with "autonomic" as above defined. Certain of the body structures are innervated wholly by one division of the autonomic system and others by the other; again, structures are activated by one division and inhibited by the other.

There are certain centers in the brain for the regulation of many important functions presided over by the vegetative system. These centers may be looked upon as being receiving and despatching stations, through which integration of action is maintained. It is here that impulses are received and transferred to the proper neurons to produce action in the terminal effector mechanisms. There is a sympathetic center in the brain, which Edinger suggested as being in the midbrain, and Karplus and Kriedl have described as lying near the tuber cinereum. It is significant that these sympathetic centers lie in the same area as those which control such functions as thermogenesis, polyuria, and vasomotor changes.

Stimuli which act upon the sympathetic system may either act on the sympathetic centers in the brain and cord, or on the true sympathetic

motor cells in the peripheral ganglia. Some evidence has been published by Camus and Roussy (*b*) which would indicate that the polyuria depending on hypophyseal disease might be due to local irritation of these centers, as will be mentioned later.

Distribution of Autonomic Components of the Nervous System.—Structures with Exclusive Sympathetic Innervations.—The following structures are believed to be supplied wholly, or almost wholly, by fibers from the sympathetic system, both activation and inhibition of action being accomplished through neurons belonging to the same system:

1. The pilomotor muscles.
2. The sweat glands. Physiologists, so far, have traced only sympathetic fibers to these structures, yet, clinically, conditions of general parasympathetic stimulation are accompanied by sweating. For this reason some students of clinical visceral neurology are inclined to believe that the sweat glands have both sympathetic and parasympathetic inervations.
3. Blood Vessels. Vasoconstrictor and vasodilator effects are both generally produced by nerves belonging to the sympathetic system. Whether constriction or dilatation occur seems to depend upon the nature and degree of stimulation. There are a few nerves, however, which do not belong to the sympathetic system, but which are definitely recognized as vasodilators, such as the *chorda tympani,* which dilates the vessels of the submaxillary glands, the *small petrosal,* which dilates the vessels of the parotid gland, the *lingual,* which dilates the vessels of the tongue, and the *nervus erigens,* which dilates the vessels of the penis. Aside from these, each spinal sensory nerve, when stimulated, has the property of causing dilatation of the superficial vessels in the zone supplied by it. This is ordinarily regarded as a true reflex effect, but there is some evidence that it may be a so-called axon reflex, mediated through peripheral structures.
4. Structures derived wholly from the müllerian and wolffian ducts; viz., fallopian tubes, body of the uterus, vas deferens, seminal vesicles, and ureter.
5. The suprarenal and thyroid glands and the anterior lobe of the pituitary.

Structures with Exclusive Parasympathetic Innervation.—There are certain structures which are believed to be supplied wholly by the parasympathetics, such as the ciliary muscle, esophagus, and cardiac end of the stomach.

Structures with Stimulatory Parasympathetic and Inhibitory Sympathetic Innervation.—The following structures are activated by the parasympathetics and inhibited by the sympathetics:—

1. The gastro-intestinal tract, both musculature and secreting glands, excepting the esophagus, cardiac end of the stomach, and sphincters.

2. Those structures derived embryologically from the gastro-intestinal tract, both musculature and secreting glands, such as:
   (a) The respiratory tract,
   (b) liver and gall bladder,
   (c) pancreas,
   (d) the body of the bladder and the muscles around the prostate gland.

3. Certain structures about the head:
   (a) The pupillary muscle,
   (b) the lacrimal glands,
   (c) salivary glands,
   (d) the gland and smooth musculature of the nose, sinuses, mouth, and pharynx.

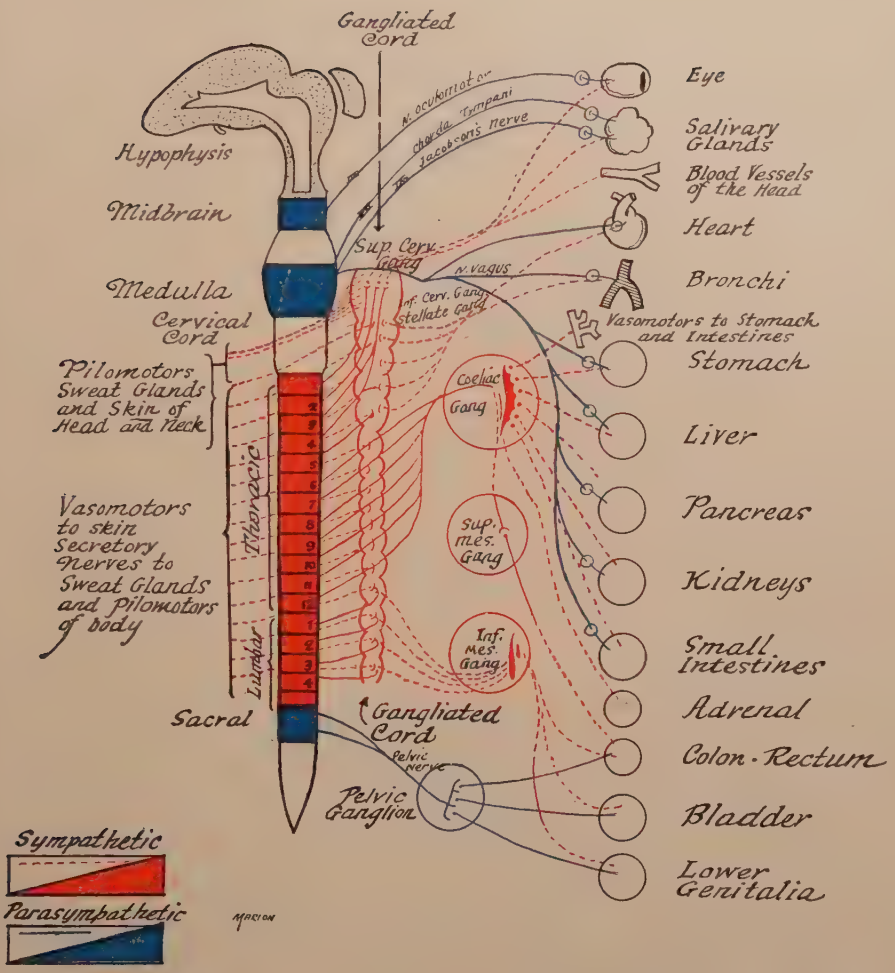
Structures with Stimulatory Sympathetic and Inhibitory Parasympathetic Innervation.—The following structures are activated by the sympathetics and inhibited by the parasympathetics:—

1. The sphincters of the gut and bladder.
2. The trigone of the bladder.
3. The urethra.

The necessity for students of endocrinology being familiar with the vegetative nerves and the action of each division upon the various tissues is evident from the fact that some internal secretions act upon one division, others upon the other, and some apparently upon both; and, since many of the symptoms which result from altered secretions of the endocrin glands depend upon the manner in which they affect the vegetative nerves, it is absolutely essential for clinicians to bear in mind that symptoms on the part of the vegetative structures must necessarily differ according to the sensitiveness of the various nerve cells to stimuli.

"Vagotonia" and "Sympathicotonia."—The medical profession is indebted to Eppinger and Hess for a valuable contribution to clinical vegetative neurology in their conception of "vagotonia" and "sympathicotonia." These clinicians have shown that by the physiologic difference in action of the sympathetic and parasympathetic neurons of the vegetative system there may be recognized two definite clinical groups, "sympathicotonic" and "vagotonic," which are met constantly in practice. In certain groups of men symptoms of predominant sympathetic stimulation exist, and in others predominant parasympathetic stimulation. These different characteristics depend on the fact that the two divisions of the vegetative system are antagonistic in action in structures which are supplied by both, and further, that each supplies certain structures alone. If the sympa-

PLATE I



Schematic illustration of the distribution of the vegetative nervous system, showing its division into sympathetic and parasympathetic components and their branches to the various organs. (Modified from Meyer and Gottlieb.)

The thoracicolumbar portion of the cord, which gives origin to the sympathetic component, is indicated in red. The portions of the midbrain and medulla, and sacral segments of the cord, which give origin to the parasympathetic component, are indicated in blue. The peripheral nerves belonging to the parasympathetics are shown as solid blue lines, while those belonging to the sympathetic system are shown as broken red lines. This chart shows the double innervation of the structures of the head, heart, and the entire enteral system, and likewise indicates the single innervation for the blood vessels, pilomotor and sweat glands.

thetic nerve cells are hyperirritable, sympathetic action predominates in the individual; if the parasympathetic nerve cells are hyperirritable, parasympathetic action predominates. Those patients belonging to the former group are called "sympathicotonic," those to the latter, "vagotonic." The term "vagotonia" is derived from the vagus, which is the most important nerve of the parasympathetic group.[1]

Manifestations of Sympathetic Hyperirritability.—Sympathetic hyperirritability (sympathicotonia) is manifested in some of the following symptoms: Dilatation of the pupil; protrusion of the eyeball; lessened lacrimal secretion; lessened salivary secretion; lessened mucous secretion in the nose and throat; lessened secretion in the gastro-intestinal tract, showing particularly as hypochloryhydria and retarded digestion; lessened motility in the gastro-intestinal tract, showing a slowness in emptying of the stomach; contraction of sphincters of the gut, and a general relaxation of the intestinal musculature leading to the common type of constipation found in the acute infectious diseases; rapid pulse and at times rise of blood pressure, although vasoconstriction in one area is usually accompanied by compensatory vasodilatation in others; increase in body temperature due to (1) vasoconstriction in the superficial vessels which interferes with the elimination of heat; and (2) an increased production of heat resulting from the increased metabolic action; diminution in the amount of urine; alimentary glycosuria; contraction of the ureter; contraction of the uterus; goose flesh; and increased sweating. Increased suprarenal, thyroid, and pituitary secretion also follow sympathetic stimulation; and this in turn produces symptoms varying in degree according to the amount of extra secretion formed.

Manifestations of Parasympathetic Hyperirritability.—Parasympathetic hyperirritability (vagotonia) is accompanied by some of the following: Contraction of the pupil; widening of the eye slits; increased lacrimation; increased secretion of the nasal, oral, and pharyngeal mucous glands, conditions commonly known as catarrh; increased salivary secretion; contraction of the laryngeal muscles, such as is met in laryngospasm; increased bronchial secretion, such as is met in bronchitis; spasm of the bronchial musculature, as found in asthma; hypermotility and hypersecretion of the gastric glands, including that of hydrochloric acid; hypersecretion and hypermotility of the intestine, leading to colicky pains and states of either spastic constipation and stasis or diarrhea, depending much on the degree of stimulation and on whether the circular or longitudinal muscles are predominantly the recipients of the increased stimulation; irritable bladder; and incontinence of urine and feces.

[1] The faulty terminology in which Eppinger and Hess's theory was originally expressed and the dubious biology incorporated in its exposition have militated against its general acceptance. While the fundamental conception seems to be a valuable one, the lack of constancy in manifestations of "vagotonia" and "sympathicotonia" detracts from clinical utility. Many more reliable data are needed.—R. G. H.

Sweating is also found in conditions which are accompanied by the above group of symptoms, as well as those belonging to the sympathetic syndrome.

Variability of Autonomic Symptomatology as Clinically Seen.—It must be evident to the most casual observer that the action of a given stimulus would differ, according to the irritability of the nerve cells acted upon; but when we consider that internal secretions are more or less selective in their action, affecting one division of the vegetative system at times to the exclusion of the other, it is further evident that the resultant action would differ greatly, according to whether the patient is a sympathicotonic or a vagotonic. With this conception grasped, one very important fact in explaining the variability of symptoms in the same disease in different individuals is established.

Hyperirritability may be general or confined to certain structures. Symptoms will often be confined to certain structures, because the nerve cells in these structures only are discharged to a significant extent. If the exciting stimulus were stronger, the symptoms would be more widespread, involving other neurons.

Intimate Relation Between the Endocrin Organs and Autonomic Nervous System.—There is an intimate relationship between the glands of internal secretion and the vegetative nerves. Stimulation of the sympathetic nerves, as before mentioned, increases the secretion from some of these glands, particularly the medulla of the suprarenals, the thyroid, and, possibly, the pituitary. Stimulation of the parasympathetics activates others. There is evidence also that the secretion from the various endocrin glands, on the other hand, activates the vegetative nervous system, some secretions, like that from the suprarenals, hypophysis, and thyroid, acting upon the sympathetics, and others, such as that of the parathyroid, ovary, and pancreas, acting upon the parasympathetics.[2]

The intimate relationship between the autonomic system and the endocrin organs has been especially emphasized by the Italian school. Pende (1916) has developed at length the conception of such relationship. Indeed, so close does he regard the functional connection that he consistently treats of the two as constituting, for practical purposes, a single mechanism.

It is assumed, says von Fürth, that the suprarenals, thyroid, and hypophysis, activated by the sympathetics, have an accelerating influence upon metabolism, stimulating protein destruction, carbohydrate mobilization, and likewise the metabolism of fats, while they also control the water and salt output and the galvanic irritability of nerves.

Clinical Significance of the Autonomic-Endocrin Relationship.—The importance of these facts is evident to the clinician who appreciates them,

[2] In case of the thyroid and suprarenal secretions only is the evidence at all convincing.—R. G. H.

and affords a basis for understanding the nervous manifestations found in endocrin disorders and endocrin manifestations found in nervous disorders. One cannot conceive of any marked change taking place in the secretion of any of the important endocrin glands, either a withdrawal, as occurs in the conditions of hypofunction, or an addition, as occurs in conditions of hyperfunction, without affecting or destroying the equilibrium of the vegetative nervous system; neither can one conceive of any marked stimulation occurring in either of the divisions of the vegetative system without affecting some of the endocrin glands.

In disturbance in the vegetative nerves, the symptoms are often expressive of stimulation of one division only, although at times there may be symptoms belonging to both divisions. Endocrin disturbances are almost always pluriglandular.

With this introduction, it can be seen that the action of the vegetative nerves and the secretions of the endocrin glands are so intimately related and correlated that they cannot be separated. Both are avenues through which action in different structures is correlated and integrated; and each in turn stimulates and receives stimulation from the other.

The Suprarenal Glands and the Autonomic System

Epinephrin and the Sympathetic System.—The secretion of the medulla of the suprarenal gland, in its relationship to the vegetative nerves, is better understood than that of any other internal secretion. This understanding has been facilitated by the determination of the close relationship which exists between the chromaphil tissue in the medulla of the suprarenal body and the cells of the sympathetic division of the vegetative nervous system, as shown by Balfour, Kohn, and Gaskell. The chromaffin [3] cells found in the medulla of the suprarenal gland are differentiated sympathetic cells, having been derived from that portion of the central nervous system which migrated from the neural canal to form the sympathetic system. They are influenced by the same stimuli that act upon the sympathetic nerves (Elliott (*b*), 1912), and *epinephrin,* the resulting secretion, influences all tissues, except the sweat glands, that are acted upon by the sympathetics, and produces the same effect as though the sympathetic nerves themselves were stimulated. This fact was finally brilliantly demonstrated by Elliott (*a*), in 1905, although foreshadowed by the results of several other investigators.

Pharmacodynamic Action of Epinephrin.—The action of epinephrin, as generally admitted, except in the case of the blood vessels, is not on the central nerve cells, but in the organ or structure itself at the myoneural

[3] *Chromaphil* and *chromaffin* are used in the literature more or less interchangeably. Historically, chromaphil has precedence.—R. G. H.

junction (Elliott, 1905). That the action is not directly upon the cells is inferred according to Macleod from the fact that epinephrin is "incapable of acting on tissues which are devoid of sympathetic nerve fibers, and is also inactive on those tissues in the embryo which have not yet received any nerve supply." Recent experiments by Hartman (1917), however, show that the action of epinephrin in the control of the blood vessels of the body may be exerted either in the dorsal root or sympathetic ganglia, as will be discussed later.

Control of Suprarenal Secretion.—Biedl (*a*) and Dreyer have shown that stimulation of the sympathetic fibers to the suprarenal glands causes an augmented secretion of epinephrin. From this fact the inference follows that any condition leading to generalized discharge through the sympathetic system leads to a similar effect. Several investigators, and especially Cannon and his coworkers, have adduced positive evidence that the emotions, pain, and asphyxia, all of which lead to generalized sympathetic discharge, cause an enhanced discharge of epinephrin. Stewart maintains, however, that none of the evidence so far offered is adequate to determine the matter. It is by such "after discharge" of epinephrin that Cannon (*b*) explains the prolonged bodily reaction to emotions after all superficial evidence of the operation of the exciting cause has disappeared. The writer has called attention (1916, 1918) to the fact that an analysis of the syndrome of toxemia, as expressed in the peripheral tissues, shows its manifestations to be a result of general sympathetic stimulation. We are justified in assuming, therefore, that toxemia stimulates the suprarenals and causes them to produce an increased amount of secretion, which augments and prolongs the effect of the nerve stimulus; and further, that severe or chronic infections may stimulate and exhaust the suprarenals.

The question of inhibition of action in the suprarenal gland is one that has interested physiologists and clinicians for a long time. Heretofore nothing definite has been known, but Cannon (1920), as a result of recent investigation, states that stimulation of the afferent vagus fibers causes inhibition of the suprarenal medulla; while stimulation of the sensory somatic fibers results in increased suprarenal secretion. This is a very important contribution.

Relation of the Suprarenals to Glycosuria.—Another interrelationship between the sympathetics and suprarenal secretion is shown in the production of glycosuria, so-called "nervous diabetes," following such conditions as grief, fright, and other forms of sudden and severe emotion. It has long been a clinically recognized fact that diabetics stand emotional stress poorly. The writer recalls a diabetic who had become sugar-free. He was playing croquet when a ball bounced and struck him on the chin. He was frightened and suffered some pain, and immediately had a return of sugar. Cannon cites the experiments of Böhm and Hoffman, who reported in 1878 that cats which were subjected to pain showed glycosuria. These cats

were treated without anesthesia. They were strapped to the holder, a tube inserted into the trachea and in some instances a catheter was inserted into the ureter through an opening above the pubis. Sugar appeared in the urine in about thirty minutes' time. They considered opening of the trachea, cooling, and pain as possible causes of the glycosuria; and inasmuch as glycosuria continued in those cases where the trachea was not opened and cooling was eliminated they concluded that the glycosuria was due to pain. Cannon repeated these same experiments and determined that pain was not the sole cause of glycosuria. Twelve cats were used in the experiment. They were bound gently to a holder and all pain was eliminated; yet it was noticed that in from thirty minutes to five hours glycosuria appeared. It was further noticed that in those animals which resisted being handled and showed fear and anger, the glycosuria appeared quickest. From this he concluded that emotion was a cause of the glycosuria, and not pain alone.

Macleod has shown that, while stimulation of the splanchnics will produce glycosuria when the suprarenals are intact, it will not when these glands have been removed. From this he infers that the effect is mediated through the secretions of the suprarenals and not through the splanchnic nerves directly.

Relation of the Suprarenals to the Vascular System.—The relationship of the tonus of the blood vessels and the sympathetic nerves, on the one hand, and the suprarenal secretion, on the other, is another interesting and important field of study. Since the action of epinephrin upon the blood vessels has become generally known, there has been a prevailing tendency to assume that it is through this internal secretion that blood pressure is maintained. This opinion was based largely on the work of Oliver and Schäfer (*b*), who showed that injections of epinephrin raised blood pressure. Swale Vincent (*a*) was one of the first to question the correctness of this generally accepted theory, and quotes the work of Young and Lehmann, who, leaving the suprarenal body, clamped off the dorso-adrenal vein in dogs, thus preventing the secretion from entering the general blood stream. They found that, "of eight experiments, there was no offect on the blood pressure in three, in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (comparable with that which follows injection of epinephrin into the circulation), lasting about three minutes. Young repeated these experiments, and found that there was an appreciable fall in pressure after the blood had been excluded from the circulation for several hours.

More recent experiments have shown that epinephrin dilates some vessels, even when given in physiologic doses, and further, that the effect in a given structure depends upon the size of the dose. This proof has been furnished by the work of Hartman and collaborators and Hoskins and his coworkers, and shows, further, the close relationship between the

action of stimulation of the sympathetic nerves and epinephrin. Inasmuch as the tonus of the blood vessels depends, with a few exceptions, upon the sympathetic nerves alone, the degree of constriction and dilatation must depend upon the nature and degree of stimulation; so does the action of epinephrin in the various vessels depend upon the dosage. Cannon and Lyman (*b*) demonstrated that cats, as a rule, respond by a fall in blood pressure when small doses of this substance are administered. Compensation is a law which operates throughout the organism, maintaining the physiologic control. Vasodilatation in some vessels must be compensated by vasoconstriction in others, or the organism would be seriously injured; and this occurs, whether the stimulus comes directly through the sympathetic nerves or through epinephrin. Hoskins and McClure (*a*) (*b*) have determined that in a dog approximately one-fourth of a cubic centimeter of a 1:1,000,000 solution of epinephrin leaves the gland per minute; but that it requires two-fifths of a cubic centimeter of 1:500,000 dilution to influence blood pressure; therefore, only one-fourth enough is regularly secreted. The primary effect of this quantity is a depression, and it requires about five times as much to raise pressure. Therefore, they conclude that only one-twentieth of the amount of epinephrin is regularly secreted that is necessary to raise blood pressure, and that such a pressor effect is produced by it only in times of stress.

That there is a shifting of the blood from the splanchnic region to the skeletal muscles has been shown by Hartman. Hoskins, Gunning, and Berry showed further that the skin vessels constrict while the skeletal muscles dilate. These authors have shown that doses of epinephrin which dilate the vessels of the skeletal muscles contract the splanchnic vessels, and also the reverse. This fact furnished evidence from which we infer that there is a general shifting of vasomotor control, according to the degree of stimulation, whether the stimulus is primarily endocrin or sympathetic.

The work of Gruber pointed to the fact, which has since been elaborated by Hartman and his coworkers, that the action of epinephrin upon the blood vessels is through the sympathetic motor cells, and not at the myoneural junction, as is accepted for other sympathetically innervated structures. They have shown that vasodilatation in the intestine and limbs is prevented by cutting the nerves to these organs; and have further located the vasodilator mechanism for the intestine in the "collateral sympathetic ganglia, probably the superior mesenteric," and for the limb in the "dorsal root ganglia and sympathetic ganglia."

Hoskins, Hoskins and McClure, Swale Vincent, and Stewart and Rogoff (*a*) (*b*) have expressed doubt whether epinephrin is of any use to the animal in its normal state. Cannon and de la Paz, however, have offered evidence that it is an important factor in integrating the body during great emotion.

The Thyroid Gland

The interrelationship between the vegetative nerves and the thyroid gland on the one hand, and the secretion of the thyroid and the vegetative nerves on the other, is not as clear and definite as that between these nerves and the suprarenals.

Control of Thyroid Secretion.—Cannon and his coworkers (1916) have done much to clarify the relationship of the vegetative nerves to the gland. After satisfying themselves that certain electrical reactions are due alone to secreting processes, they proceeded to investigate the thyroid, and show by the development of an action current that the sympathetic nerves which are distributed to it supply its secretory fibers. Stimulation of the vagus fibers to the thyroid, on the other hand, failed to cause any action current in the gland; hence it was concluded that these fibers have no control on the secretory processes, as has been claimed by Asher and his coworkers. To further test this experimental result, they first injected epinephrin (one-tenth to one-fifth of a 1:100,000 dilution) in a cat and produced the electrical reaction indicative of secretory activity. Then the splanchnic nerves to the suprarenals which had previously been separated from their connection with the central nervous system were stimulated to bring about discharge of epinephrin. Again an action current was detected in the thyroid. These experiments seem to show definitely that the sympathetic fibers are the secretory nerves of the thyroid, and further, to establish the basis for the accepted fact of the close relationship between the secretion of the suprarenals and the thyroid.

Clinical Significance of the Thyroid-Sympathetic Relationship.—Clinically this close relationship is sometimes evident and sometimes not, the reason for which must be plain to any one who appreciates the complexity of clinical reactions. One can, when working experimentally, apply a stimulus definitely to a given organ or structure. Under clinical conditions, however, a given stimulus is frequently not directed to a single organ or tissue, but expends itself upon the organism as a whole, producing widespread reactions. A multiplicity of such stimuli may produce complex syndromes.

The effect of the major emotions in stimulating the sympathetics, as shown by Cannon (1915), lays an experimental basis for the observation made by clinicians that conditions of hyperthyroidism often follow emotional excitement, a point which has been particularly emphasized by Crile. The same ground for a hypersecretion exists in cases of toxemia; for toxemia expresses itself peripherally through the sympathetics. In this way we can see how such conditions as tuberculosis (Pottenger) (*a*) (*b*) (*c*) (*d*), syphilis, and intestinal toxemia (McCarrison), and infections

of the digestive and urogenital tract (McCarrison; Barker (*b*)) influence this gland. We can further see that a source of the loss of weight in these conditions may be an increased metabolism produced by the increase in the thyroid secretion, which hastens the catabolic processes in the tissues by acting as a catalytic agent in the tissue cells themselves, and, according to Plummer, controlling the energy output. Thyroid substance, however, not only increases catabolism, but, as Janney (*b*) shows in case of cretins, it has an anabolic action as well.

The Goetsch Test for Hyperthyroidism.—The thyroid secretion is a sympathicotropic secretion, and, as Oswald (*b*), Cannon and Levy have suggested, has the property of sensitizing the sympathetics; in other words, it makes the sympathetic nerve cells respond to stimuli more readily than is normally the case. Goetsch (*b*), taking advantage of this fact and the further fact that epinephrin selectively stimulates the sympathetic system, has suggested that hyperirritability shown on the part of the sympathetic nervous system to a comparatively small dose (one-half a cubic centimeter) of epinephrin may be taken as evidence of hyperthyroidism.[4] From the standpoint of visceral neurology, this test must be considered as an indication of sympathetic hyperirritability; since the thyroid hormone is sympathicotropic, its presence in excess should be accompanied by such sympathetic hyperirritability, and, if other sympathicotropic stimuli can be ruled out, hyperthyroidism should be suspected.

The secretion from the thyroid, when discharged in excess, produces a train of symptoms which affect the entire organism—the nervous system, both voluntary and vegetative, other endocrin glands, and the entire psychical and physical being.

Sympathetic and Parasympathetic Hyperirritability in Graves' Disease.—In the discussion of Graves' disease, von Noorden, Jr., describes two types, according to whether the symptoms are predominantly those of sympathetic or parasympathetic stimulation. The presence of a group of the following symptoms is characteristic of the parasympathetic (vagotonic) type; a relatively slight degree of tachycardia, with, however, markedly pronounced heart oppressions, distinctly marked *v. Graefe's* sign, and wide palpebral fissures, absent *Moebius'* sign, slight protrusion of the eyeballs, marked secretion of tears, outbreaks of sweat, diarrhea, disturbances in respiratory rhythm, and absence of alimentary glycosuria. Some of the following symptoms are characteristic of the sympathicotonic type: marked protrusion of eyeballs, greatly increased cardiac activity with slight accentuation of subjective disturbances, absence of sweats and diarrhea, marked falling out of hair, inclination to increase of tempera-

[4] *Hyperthyroidism* is frequently used in the clinical literature to include, not only the condition resulting from so-called toxic adenomata in the thyroid, but also exophthalmic goiter. Janney and others have emphasized the possibility that, in the latter condition, the term hyperthyroidism is a misnomer—that the condition is *dysthyroidism*. The Goetsch test is positive in both conditions.—R. G. H.

ture, absence of eosinophilia, no disturbance in respiratory rhythm, and alimentary glycosuria.

It has long been taught that the thyroid secretion, when in excess, sensitizes the nerve cells, and particularly those of the vegetative system, as shown by Cannon and his coworkers. We find a hyperirritability of the same cells in states of psychic perturbation generally, and psychical disturbance is more or less prominent in hyperthyroid cases. I cannot help thinking that the psychical condition of the patient is responsible for many of the clinical symptoms of the disease. In speculating as to the reason why at one time the symptoms should be those of vagotonia, and at another those of sympathicotonia, I would suggest that symptoms are prone to appear on the part of that division of the vegetative system in which the irritability of the cells is most marked. Aside from this, however, we must not lose sight of the fact that there seems to be a mutual reaction of the secretions from the suprarenal and thyroid. Since both of these secretions are sympathicotropic, it may be inferred that the thyroid secretion naturally has the greater affinity for the sympathetics.

Changes in Sympathetic Ganglia in Graves' Disease.—Another very interesting relationship between the cervical sympathetics and the thyroid is suggested by the studies of Jaboulay, Wilson and Durante, and Wilson, in which histologic changes were found in the cervical sympathetic ganglia in hyperplastic toxic goiter. We can only speculate as to the relationship between the condition in the gland and that in the thyroid. Does one depend on the other; and which is primary? Stimulation of the cervical ganglia can produce exophthalmos, rapid heart, and increased activity on the part of the thyroid, so it seems that, if there is a causative relationship, the gangliary changes probably stand as the cause. In this connection, the experiment of Cannon, Binger, and Fitz, in which they succeeded in producing exophthalmos, tachycardia, and increased body metabolism in a cat by joining the phrenic nerve to the cut cervical sympathetic, is of especial interest.[5]

The Autonomic System in Hypothyroid States.—The relationship of the thyroid secretion to the nervous system may be further studied in cases of withdrawal of the substances, either experimentally, or, as we find it clinically in cretinism and myxedema, or in the milder hypothyroid states.

In these conditions certain inhibiting disturbances in the normal action of the sympathetics is evident. The skin may be dry, the hair lusterless with a tendency to premature grayness, the pulse slow, the circulation sluggish, and the metabolic rate reduced. The patients feel cold and actually may have subnormal temperature. Injections of epinephrin may fail to produce glycosuria and pilocarpin fail to produce sweating.

The parasympathetics are also below the normal in excitability, but

[5] Langley, years ago, and several observers since have failed to secure successful results in this experiment.—R. G. H.

apparently not to the same extent as are the sympathetics. In fact, the general nature of this disease is such that the excitability of all of the nerves, both voluntary and vegetative, is reduced. In hypothyroid conditions the psychic activities also are depressed. The patient is sluggish in thought and action, slow of speech, and shows an unusual desire for sleep.

The Hypophysis and the Autonomic System

The hypophysis or pituitary is made up of three parts, the *pars anterior, pars intermedia,* and *pars nervosa.* These three parts are different in structure and function. The *pars anterior* is supplied by sympathetic nerves, which, according to Bell, were first fully described by Berkeley. While the *pars nervosa* has many neuroglia cells and fibers, yet Bell (*c*), writing in 1919, says: "No evidence has yet been adduced to show that the sympathetic nerves leave the blood vessels in the *pars nervosa* as in the case of the pars anterior. It has been suggested, however, that such fibers may possibly reach the *pars intermedia* from the pars anterior." Weed, Cushing, and Jacobson and Shamoff have adduced evidence that stimulation of the superior cervical sympathetic causes increased secretion. This, according to the first mentioned observers, may result in glycosuria.

The relationship of the pituitary to the vegetative nerves is far from clear. While the gland is considered as belonging to the same group as the suprarenals and thyroid, and to be sympathicotropic in action, the symptoms which arise from injecting products of the gland are partly to be attributed to sympathetic stimulation, and partly to parasympathetic.[6] The effect on the vascular system varies according to the dosage, the same as it varies according to the degree of stimulation of the sympathetic nerves. On this account, Bayer and Peter think that there must be two active principles responsible for these various and opposing symptoms. As a result of injections of an extract of the pars intermedia and pars posterior, the following effects have been noted: the vessels are constricted (Oliver and Schäfer); the heart may be slowed as a result of contraction of the peripheral vessels (Howell); diureses is produced[7] (Magnus and Schäfer); contraction of the bladder takes place (v. Frankl-Hochwart and Fröhlich); no effect is produced on the resting uterus, but marked contraction of the menstruating or pregnant organ (Dale (*a*), Bell and Hick, and Bell (*a*)); there is marked contraction of the stomach and intestinal musculature (Bell); an increase in gastric secretion (Houssay and Maag); an increase of the secretion of the mammary gland (Ott and Scott); an

[6] Most of the effects of hypophyseal extracts are due, according to the best evidence now available, to stimulation of the tissue cells directly—R. G. H.

[7] This is true under certain experimental conditions only. The use of pituitary extract to relieve the polyuria of diabetes insipidus is an illustration of a contrary effect.—R. G. H.

inhibition of pancreatic secretion (Pemberton and Sweet); and a glycogenolytic action (Cushing (*d*)).

It will be seen that the action on the blood vessels, of the kidney in the production of diuresis, and the inhibition of the pancreatic secretion are symptoms which may be produced by stimulation of the sympathetic nerves; the remaining symptoms, on the other hand, are those of parasympathetic stimulation.

Bell showed that an isolated uterus, suspended in Ringer's solution, contracted on the addition of infundibulin, proving that the action, at least for that organ, is peripheral. And this has been maintained by others. Kepinow thinks that the action of infundibulin extract is to sensitize the point of attack of epinephrin; but this can hardly be reconciled with the statement that the action of this extract is upon the parasympathetics, instead of the sympathetics. Cow (*b*) also has found that pituitary extracts sensitize uterine tissue to epinephrin.

I recently had an opportunity to observe a postadolescent clinical case, in which there was evidence of a slight increase in pituitary activity. The most marked symptoms were polyuria, up to 6,500 cubic centimeters per day, hyperacidity, intestinal pain of a severe degree, and an increase in metabolic rate, resulting in a loss of weight which was difficult to restore, even on rest and excessive diet.

The Pancreas and the Autonomic System

Nervous Control of the Pancreas.—Embryologically the pancreas belongs to the enteral system, being derived from the intestine. Therefore, it carries with it the innervation of the intestine. Its glands of external secretion are stimulated to action by the parasympathetics (vagus) and inhibited by the sympathetics. Aside from the pancreatic juice, the pancreas is recognized as producing an internal secretion. Whether or not stimulation of the vagus increases this secretion too, we have no direct evidence. This secretion is generally believed to be produced by the islands of Langerhans. It is of particular interest, because of its influence upon the glycogenic functions of the body.

Puncture Glycosuria.—The relation of the pancreatic hormone to glycogenesis must be discussed along with the nervous control of this function. Claude Bernard determined by experiment that a puncture (piqûre) in a certain place in the floor of the fourth ventricle causes glycosuria. This experiment definitely determined that there is a nervous control of the glycogenolytic function. It has more recently been shown that the nerve control of glycogenolysis rests in the sympathetic nerves, and that impulses which cause glycosuria travel over the splanchnics. Puncture glycosuria could be accounted for as being due to injury to the sympathetic

center near the tuber cinereum. Factors which cause marked stimulation of the sympathetics, such as the major emotions, as shown by Cannon, are followed by glycosuria.

Hormone Factors in Glycogenolysis.—Not only is glycogenolysis favored by stimulation of the sympathetic nervous system, but also by hormones produced by certain glands of internal secretion, particularly the suprarenals, thyroid, and pituitary. It will be noted that these glands are particularly identified with the sympathetic nervous system. Hyperfunction on their part may be accompanied by glycosuria. This is especially well recognized in case of the suprarenals and thyroid. An observation which was first made by Ludwig and Kraus, that certain cases of hyperthyroidism show glycosuria, has been explained by Eppinger as being in patients of the sympathicotonic type; on the other hand, glycosuria should not be expected to occur in the vagotonic. Hypofunction on the part of the thyroid is likewise followed by hypoglycemia. Janney (*a*) says: "The clinical occurrence of the low blood sugar values in diseases presenting hypofunctional condition of ductless glands (cretinism, myxedema, Addison's disease, hypopituitarism) unmistakably indicates the general significance of these symptoms."

Macleod and Pearce have shown that splanchnic stimulation fails to produce hyperglycemia in animals from which the adrenals have been previously removed. At the same time Macleod does not believe that glycogenic disturbances can be wholly divorced from the sympathetic nerves and attributed wholly to epinephrin action, and cites the fact that stimulation of the previously cut nerves of the hepatic plexus in a normal animal, without any stimulation of the adrenals having occurred, produces hyperglycogenolysis.

V. Furth and Schwartz reviewed the experiments and suggestions of Zülzer and von Noorden as to the antagonistic action of the chromaffin tissue and the pancreatic hormone, and came to the conclusion that such an antagonism exists.

Sometimes disease of the hypophysis is accompanied by glycosuria. An explanation of this, aside from a hormone action, has been offered by Aschner (*a*) (*b*), who suggests that the glycosuria is produced by stimulating the sympathetic nervous center, which Karplus and Kreidl have shown to exist near the tuber cinereum.

From this discussion it may be assumed that the cause of glycosuria is bound more or less complexly with the hormone produced in the pancreas, on the one hand, and the sympathetic nerves and the endocrin glands related to it, particularly the suprarenals, pituitary, and thyroid, on the other hand. Whether the absence of the pancreatic hormone, when the islands of Langerhans are destroyed, allowing the sympathetic system and the sympathicotropic hormones to functionate unopposed, is a small or large factor in the cause of diabetes, is not fully determined. Neither do

we yet know the importance to be attached to the presence of this hormone in sugar metabolism.

The Gonads and the Autonomic System

Nervous Manifestations Following Castration.—It is extremely difficult in the present state of our knowledge to discuss, in an intelligent manner, the relationship between the sex glands and the vegetative system. Both ovaries and testicles are innervated by sympathetic nerves, and the secretion from the testicles, according to Wheelon (*a*)(*c*), is sympathicotropic, while that from the ovary seems to be different, as shown by Hoskins and Wheelon. Castration of males caused a lowered irritability of the sympathetic system, whereas spaying of females caused a heightened irritability of the same system. Wheelon and Shipley estimated that castration of males lowered sympathetic irritability by fifty per cent. The internal secretion of the ovary, or at least that of the corpus luteum, is also sympathicotropic, if we may judge from the clinical symptoms which appear preceding the menstrual flow and those at the beginning of pregnancy or after oöphorectomy, when the menstrual cycle suddenly ceases, or at the climacteric, when the secretion is gradually withdrawn. During the latter half of the menstrual cycle the secretion from the ovary exerts a marked nervous and psychical influence upon the patient. This influence, as expressed through the vegetative nervous system, seems to be preponderantly that of sympathetic stimulation. The pulse usually increases in rapidity, the blood pressure becomes higher, the temperature is elevated, and a slight neutrophylic hyperleukocytosis is noted. While these symptoms may be evidence of increased sympathetic stimulation, we cannot claim that they are wholly due to direct stimulation of the sympathetic nerves, because this physiologic process makes an impression upon other organs of internal secretion, such as the thyroid, pituitary, and suprarenals, and upon the nervous system as a whole, and, probably most of all, upon the psychical centers. Immediately following the commencement of the flow, a general relaxation of tension takes place. Nervous and psychical irritability disappear, the pulse becomes less frequent, the temperature drops, and blood pressure falls.

Clinical Manifestations of Disturbed Gonadal Endocrin Functions.—At the beginning of pregnancy, or during the establishment of the menopause, either artificial or natural, we see the opposite picture. The secretion from the ovary is suddenly or gradually withdrawn and the body is forced to readjust itself to new conditions. Again, a state of nervous and psychical excitability is experienced (Pottenger, 1917). The picture, however, is different. The symptoms are predominantly those of parasympathetic stimulation (vegetative) such as nausea, vomiting, spastic

constipation, hyperchlorhydria, colicky pains, low pulse tension, and sometimes slow pulse. Again we must repeat that these symptoms are variable, because they are very complex in their causation, being a resultant of nervous, psychic, and endocrin reactions.

Another very important clinical observation, which has been dwelt upon by Bell, is that patients pass the menstrual cycle, the beginning of pregnancy, or the menopause, either normal or artificial, differently, according to whether they have large, small, or medium amounts of ovarian secretion. A woman classed as hypo-ovariac has very different premenstrual symptoms from one who is hyperovariac. In fact, she may have vagotonic symptoms instead of sympathicotonic. The hypo-ovariac also is likely to enter upon pregnancy or the menopause with comparative comfort, for the withdrawal of the ovarian secretion makes a comparatively slight impression. The hyperovariac, on the other hand, suffers the loss of a very dominant secretion, apparently sympathicotropic as far as the menstrual cycle is concerned, and consequently suffers from excessive parasympathetic irritability (vagotonic) on the part of many structures. The withdrawal also profoundly affects the patient psychically, disturbing the equilibrium in those structures that are particularly prone to show endocrin and nervous imbalance. Laignel-Levastine has described many of these nervous, psychic, and endocrin relationships as they appear clinically.

The Parathyroids and the Autonomic System

Little can be found in literature regarding the relationship between the parathyroids and vegetative nerves. The principal nerves to these glands seem to be those branches of the sympathetics which supply the blood vessels, yet I find no recorded experiments which purport to establish the secretory nature of these nerves.

While the internal secretion of the parathyroids seems to act chiefly upon the central nervous system and produces the disease known as tetany, the vegetative nerves also come in for a disturbance in equilibrium.

MacCallum and his coworkers have shown that the symptoms of tetany which result from ablation of the parathyroids may be produced by perfusion of blood from which the calcium has been removed by dialysis, and believe that the symptoms of this disease are due to a lack of calcium in the blood, which results from the failure of the secretion from the parathyroid gland.

An analysis of the symptoms in the vegetative structures fails to show a preference for either the sympathetic or parasympathetic nerves. On the other hand, there seems to be a general heightening of excitability on the part of both divisions. There seems to be a pronounced excitability of the nerves supplying the blood vessels (Falta (*c*)), as is shown by localized

anemias resulting from irritation and by the presence of pronounced dermographism. This author states that the injection of epinephrin produces an abnormal sympathetic reaction, as shown in the blood pressure, heart action, and contraction of vessels of the skin; also an abnormal parasympathetic reaction on the injection of pilocarpin, shown by profuse sweats, salivation, increase in flow of tears, hypersecretion of the gastro-intestinal tract, nausea, vomiting, and diarrhea.

The opinion seems to be generally accepted that the reduction in the calcium content of the blood increases the excitability of all nerve centers, both those of the central and vegetative systems.

The Thymus and the Autonomic System

Discussions of the thymus gland in its relation to the vegetative nervous system are very fragmentary. The thymus is usually classed as a gland of internal secretion, yet its endocrin nature is doubted by a considerable number of physiologists. Probably the strongest evidence of its production of an internal secretion has been furnished by Uhlenhuth (*c*) (*d*) (*e*) (*f*). His experiments indicate that it produces a substance which causes tetany, and which is counteracted by the parathyroids. But, on teleological grounds, the existence of such a function is doubtful.

Certain symptoms have been described in hyperplastic conditions of the thymus, such as "thymic asthma," hoarseness, stridor, dyspnea, and eosinophilia, which cannot all be accounted for on the ground of pressure, and which have caused Wiesel (*b*) to suggest that the thymus probably supplies the blood with a parasympathicotropic substance. The thymus is classed by many investigators as a parasympathicotropic gland.

Hormone Factors in Growth and Development . . . . . .

. . . . . *Eduard Uhlenhuth*

The Relation of the Thyroid to Growth and Development—Of the Hypophysis Cerebri—Of the Sex Glands—Of the Thymus.

Hormone Factors in Growth and Development

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NEW YORK

Introduction

Among the problems that present themselves in the study of living organisms, one of the most fundamental, fascinating, and yet obscure is that regarding the mechanism involved in the production of organic form. Why does living matter assume the forms and structures that it does? Important progress has been made in recent years in elucidating the relationship existing between life and the visible form to which it attaches itself. Most helpful in this respect was the knowledge gained by the discovery of the internal secretions, through which it became known that definite organic structures are related to definite specific substances. The greatest progress along this line came from the discovery of the thyroid hormone, the relation of which to growth and development is well established. According to the knowledge which we possess at present, it would seem that a whole series of new morphological structures arose, phylogenetically speaking, in the amphibians as a result of the thyroid hormone, and it is probably upon this basis that the entire development of the higher vertebrates has proceeded. This instance will serve to illustrate the importance of the internal secretions in the development of organisms. Similarly well known is the establishment of the secondary sex characters through the action of the sex hormones. It is certain that internal secretions played a large rôle in the formation of animal organisms; rudiments of the endocrin glands are found already in the crustaceans (Patten), and there are reasons to assume the action of internal secretions in organisms as low as the insects (Bordage).

It should be kept in mind, however, that the internal secretions constitute only one group of specific substances, the morphogenic action of which has been recognized as one of the main principles in the development of organisms. The important rôle of specific substances in the morphogenesis of the organisms was emphasized by the botanist Julius Sachs, and recently by Jacques Loeb. In the experiments of the latter made on *Bryophyllum* he demonstrated this rôle as regards various organs

of the plant. He was able to indicate the existence of specific substances necessary to the production of leaves and roots, and showed that quantitative relations exist between the organ and the substance producing it; more and larger organs are produced as a greater quantity of the substance is supplied at the place of growth.

Little is known as to the mode of action of the internal secretions, although we do know, through the discoveries of Kendall, that the thyroid hormone acts as a catalyser and augments the metabolic process in an effective and specific manner. If this be the only peculiarity of the thyroid hormone, by means of which it produces new structures, it may mean that mere *quantitative* differences are perceived by our sense organs as *qualitatively different* morphological structures. This view fits in well with observations of Child on diverse groups of organisms. According to this author, the qualitative differentiations along the various axes of an organism are simply the expression of quantitative differences of metabolism. For instance, the formation of the head, according to Child, takes place wherever in an organized living system a metabolic maximum is formed.

Among the endocrin glands only the thyroid, the pituitary body, and the sex glands are definitely known to control growth or development, or both. These three glands and the thymus will be discussed in this article. Although the thymus gland seemingly does not actually play any rôle in growth and development, it has been thought well to include it here because of a widespread belief that it has such a function.

The Relation of the Thyroid to Growth and Development

In the quadruped vertebrates the presence of the thyroid gland is absolutely necessary for normal growth and development of the organism, though the absence of this gland, at least in the lower quadrupedes is not incompatible with the maintenance of life. It is probable that not only the ontogenetic development of the individual is controlled by the thyroid hormone, but that even the phylogenetic development of a large group of organisms containing the most highly organized animals and man was initiated through the acquisition, by the amphibia, of the thyroid mechanism in the condition as we find it to-day in these animals.

Before entering upon the subject it is perhaps well to point out that most of the morphogenetic effects brought about by the action of the thyroid can best be understood if we assume that they are the particular response of the inherited physicochemical structure of the organisms to an agent having the peculiarity of increasing the rate of chemical reactions more than any other known substance. That the thyroid hormone

increases metabolism is well known (Magnus-Levy, Schöndorff, Mayerle and numerous more recent investigators) and Kendall, who succeeded in isolating the probably pure thyroid hormone (thyroxin) and determined its chemical constitution, possibly found an explanation why this substance should so efficiently raise the metabolism. According to Kendall (*c*) 1/3 mg. of thyroxin increases the basal metabolism of an individual of approximately 150 pounds by 1 per cent. Since Baumann discovered that the active principle of the thyroid contains iodin, much has been speculated about the rôle of this iodin. Kendall (*c*) thinks that the presence of iodin in the thyroxin merely renders the active groups of this compound more reactive, but that it is not used as such in the metabolic processes. In accordance with this opinion is the fact that the more iodin the thyroid substance employed in the experiment contains (Lenhart, Graham), the more effective is thyroid feeding in bringing about certain changes in tadpoles presently to be discussed, while most iodin compounds other than those contained in the thyroid, and especially the inorganic, have no effect (Morse) on development. Also as regards the physiological effects certain organic iodin compounds, such as gorgonin and spongin, though they contain far more iodin than does the iodothyroglobulin prepared from the thyroid, are less effective than the latter substance (Oswald). Recently it has been demonstrated, however, that at least some organisms are able to utilize the inorganic iodin in the morphogenetic processes without the intermediation of a thyroid gland (Swingle (*b*)). We shall later revert to these experiments. So far as the morphogenetic effect of the thyroid hormone is concerned, the most important question, it seems to me, is that as to the changes which it effects in the metabolism. Does the thyroxin actually, as Kendall claims, merely increase the reactions going on also without it in the organism, without changing or adding any reactions and must we think that a mere quantitative change is able to produce all that multitude of new forms and structures that we see arise in a thyroidless organism after the administration of the thyroid hormone?

Relations in Mammals.—The effects of the thyroid hormone upon the development of the mammals, as far as they have been studied, are probably well known to most readers of this handbook and will be discussed here only briefly. They can be studied in various ways. Important information was obtained from the study of human subjects who in prepuberal periods of life developed hypo- or a-thyroidism (for literature see Falta (*a*)). The most conspicuous consequences of thyroid deficiency are the nearly complete cessation of growth, a lack of proper ossification of the skeleton, in consequence of which the epiphyses of the limb bones remain separated, disturbances in the development of the teeth, retention of an infantile condition of the sex organs and failure of the brain to develop beyond an infantile condition. Administration of thyroid preparations

in such persons (cretins) may bring about a renewal of growth and development. In mammals the condition of athyroidism was produced by removal of the thyroid gland soon after birth (Hofmeister, Eiselsberg (*b*), Biedl (*b*) and numerous other investigators). The results are very similar to those produced by a-thyroidism in man. Growth ceases at an early date after the extirpation, the skeleton is incompletely ossified, the thymus does not show the involution accompanying development of the normal organism and the sex glands remain hypoplastic. Frequently the animals die from emaciation (cachexia thyreopriva).

Like all the processes of growth, regeneration, too, is greatly diminished after removal of the thyroid. This was shown by Marinesco and Minea and by Walter, who cut the nerve after removal of the thyroid and studied the process of regeneration. It is interesting to note that not only regeneration is greatly delayed, but that even the degeneration of the cut ends, which under normal conditions follows very quickly, proceeded at a very slow rate, due to the retardation of all metabolic processes.

Feeding thyroid gland to mammals results either in an increased or decreased rate of growth according to whether a small or a large dose is used. Lately E. R. Hoskins (*a*) has made careful observations on the effects of feeding thyroid to rats and has given a full review of this subject. Among the earlier observers Bircher found that one of the most conspicuous effects of feeding thyroid substance to mammals is the early calcification of the long bones, a fact that corresponds to the opposite phenomenon in thyroidless mammals. In general, however, the effect of feeding thyroid to the normal organism is less conspicuous than the changes that occur in cretins after administration of thyroid substance. It is possible that the organism when in possession of a normal thyroid gland is able to regulate in some way the amount of hormone circulating in the blood, even if there be introduced an excess of it from outside.

Relations in Amphibia.—Far more conspicuous than in mammals are the morphogenetic effects of thyroid feeding in amphibians. A large mass of facts as regards the influence of the thyroid upon growth and development in amphibians has accumulated since the publication of Gudernatsch's famous experiments on the larvæ of frogs and toads and, in fact, the consequences of thyroid feeding have been studied far more completely in amphibians than in any other group of animals. In 1912 Gudernatsch (*a*) discovered that feeding thyroid gland to tadpoles hastens development to such an extent that metamorphosis may take place within a few days after the first administration. These experiments have been repeated by many authors (Romeis, Kahn, Abderhalden, Allen, Swingle (*a*), E. R. Hoskins) and always have given the same striking effects. Similarly, in the caudate Batrachians such as the salamanders, feeding of thyroid or keeping the larvæ in a suspension of iodothyrin results in rapid trans-

formation of the larvæ into terrestrial salamanders (Laufberger, Uhlenhuth (*g*), Jensen, Kaufman). In tadpoles the effect of the thyroid feeding as described by Swingle (*a*) consists in an accelerated development of the hind and fore limbs, in a rapid reduction of the tail, in the precocious differentiation of the simple coiled intestinal tube into the stomach, small and large intestines and rectum of the adult, in the precocious development of the frog mouth and of the protrusion of the eyes. In salamanders the effect of the thyroid feeding consists, so far as is visible, externally, in rapid loss of the gills and of the fin of the tail and in shedding of the entire skin.

In the earlier experiments (Gudernatsch) relatively large doses were employed; this resulted, in spite of the accelerated development, in cessation of growth and even in diminution of size. Lenhard showed, however, that small doses when administered with an abundant supply of food, especially carbohydrates, do not lead to diminution of size, but, on the contrary, accelerate growth. The explanation would seem to be that if large doses are administered, metabolism is increased to such an extent that the animal cannot supply the excessive demand by the food intake alone and draws on the tissues of its own body to build up the rapidly differentiating new structures.

In spite of the rapid progress of differentiation of nearly the entire body there are, however, some organs that seem to remain unaffected by the thyroid application. In the thyroid-fed tadpoles the sex glands do not develop more rapidly than in normal larvæ (Swingle (*a*)). In salamanders, metamorphosis of the thyroid-treated larvæ may occur without development of the pigmentation of the adult (Uhlenhuth (*i*), Jensen) and of several toes that were not developed before administration of the thyroid substance was begun (Uhlenhuth (*i*). It is, therefore, not unlikely that the development of these organs is controlled by substances other than the thyroid hormone, but which are produced by the action of the thyroid hormone, and which act more slowly than the latter.

Recently a method has been devised to extirpate the thyroid gland from tadpoles at an early embryonic stage (Allen (*a*) (*f*) (*g*), Hoskins (*a*) (*b*)). The results of the extirpation experiments are in perfect accord with those obtained by feeding the gland and were described by Allen, Terry, Rogers and Hoskins. In the beginning, the larvæ show normal development; but at the time when the hind limbs appear in the controls, the thyroidectomized larvæ begin to fall behind the controls. The thyroidectomized larvæ never do metamorphose, but may develop hind and fore limbs that are larger than those of metamorphosing larvæ (Allen (*f*); the fore limbs, however, never break through the skin. This may be due, as suggested by Uhlenhuth (*i*), to the fact that in the absence of the thyroid the changes of the skin that lead to the shedding of it do not occur and that consequently the fore limbs are not freed. The ossification of the skeleton is stopped and at the same time growth of the long bones is re-

tarded (Terry). The thymus gland, though its structure develops like in a normal larva, does not migrate to the position that it has in adult frogs, nor does it degenerate like that of a normal frog. The sex glands show a behavior opposite to that observed in thyroid-fed larvæ; while most of the organs (coiled intestinal tube, brain, mouth, skeleton, thymus, etc.) exhibit a marked retardation or even complete inhibition of development, the sex glands develop exactly like those of normal larvæ (Allen (*g*)). This behavior corresponds well to that of several species of salamanders that normally remain permanently larval but develop the sex organs to a mature stage and breed while larvæ. This shows again that the development of the sex organs is not controlled by the thyroid hormone, at least in the amphibians. Similarly, the skin, in many species of salamanders, may develop even though development of the rest of the body is checked (Uhlenhuth (*i*)). Particularly interesting in this respect is the behavior of the eyes. In man protrusion of the eyes is abnormal and results from a disturbed function of the thyroid (exophthalmus in Basedow's disease). In amphibians, on the other hand, exophthalmus is a normal characteristic, which begins to appear as a rule at the time of metamorphosis. But it may also develop in animals that for some reason do not metamorphose, as, for instance, in thymus-fed salamander larvæ. Kaufman (*b*) has therefore suggested that the exophthalmus may not be produced by the normal thyroid secretion, but by the escape of some toxic substances from the thyroid in the absence of the normal process of the elaboration of the hormone (see also Uhlenhuth (*h*)).

While in mammalians athyroidism is pathologic, in one American species of amphibians, *Typhlomolge rathbuni,* no thyroid is found (Emmerson). This animal, which inhabits certain cretaceous caves in Texas, behaves as we would expect from the results of the extirpation experiments; it remains, during its entire life, in a larval condition and many of its organs are only poorly developed or atrophied; yet the sex organs develop normally and reach maturity while the rest of the animal is in an infantile condition. The Typhlomolge is of special interest, also, because it demonstrates at what a phylogenetic stage the amphibians and perhaps the entire higher vertebrates would be if they had not developed the thyroid mechanism. For this reason I cannot agree with Smith, who thinks that the thyroid hormone in causing metamorphosis does not produce anything new, but simply by increasing the metabolism merely accelerates a process that would occur in any case, but at a slower rate. On the contrary, even if the thyroid hormone does not do anything else but change the metabolism in a quantitative way, the Typhlomolge as well as the thyroidectomized tadpoles show that this mere quantitative change is able to create in a definite physicochemical system supplied by heredity new morphological characters that could never have been developed in the absence of the thyroid mechanism.

Relation of Iodin to Developmental Processes.—Swingle (*b*) (*c*) (*d*) (*e*) has discovered that in tadpoles inorganic iodin has the same effect of bringing about precocious metamorphosis as has thyroid substance. In fact, Swingle (*b*), and Allen (*j*) showed that even in thyroidectomized tadpoles iodin can bring about metamorphosis. Swingle, therefore, claims that the iodin is the effective principle in the thyroid hormone. There are, however, several reasons that make this conclusion doubtful. It is possible that in the amphibians the centralization of the thyroid function is not yet so far carried through as in mammalians and that in the amphibian organism perhaps all cells possess the ability of elaborating the thyroid hormone if they are supplied with enough iodin. Or it may mean that there is, in the amphibian body, in addition to the thyroid another organ that may be able, in the absence of this gland, to produce a compensating (or identical) hormone. In favor of this view are the experiments made by Hoskins (*c*) which show that, in complete absence of the thyroid, feeding of hypophysis is able at least to initiate and in some cases even to complete metamorphosis. Allen's experiments, indeed, seem to show that in amphibians the functions of thyroid and hypophysis are very much alike; the differences between these two organs having not reached the high degree as they present in mammals. It is furthermore possible that in the amphibian organism the metabolic mechanisms have not yet been so far specialized as in the mammalians and that consequently these mechanisms are able to react not only to the thyroid hormone but to many other substances. In favor of this would be some results recently reported by Laura Kaufman (*b*), according to whom other substances known to increase metabolism, such as salicylic acid, are able to cause metamorphosis of the axolotl; before drawing further conclusions, however, it seems necessary to repeat Kaufmann's experiments. That the effect of the iodin in tadpoles must be due to some peculiar mechanism in these animals and may, therefore, not permit of any general conclusions regarding the rôle of iodin in the thyroid hormone is evident from the entirely different behavior of closely related animals. Uhlenhuth in as yet unpublished experiments has repeated Swingle's experiments on the effect of inorganic iodin on the development of tadpoles and has found that, as reported by Swingle, small quantities of iodin (2 to 3 drops of 1/20 m. solution in 1000 c.c. water) are able to hasten growth of the legs, development of the mouth and gut; the tadpoles are extremely sensitive to iodin and slightly larger quantities of iodin (4 to 5 drops) result in death. Regarding the quantitative effect the iodin is doubtlessly inferior to the iodothyrin, since the latter will bring about metamorphosis far more quickly than iodin. Uhlenhuth subjected salamanders also to the action of iodin compounds, but with negative results. Recently Uhlenhuth has repeated his former experiments on a larger scale and obtained the following (as yet unpublished) results. Salamanders are less susceptible

to the toxic action of iodin than tadpoles. It is possible to keep salamander larvæ in solutions of 5 drops of 1/20 m. iodin in 1000 c.c. and feed them while they are in this solution on large crystals of iodin without producing any toxic effects. If the animals are kept in 8 drops of 1/20 m. iodin and 1000 c.c. water, the movements of the animals become convulsive, though it would be possible to go still higher without killing them; feeding too large crystals of iodin results in death. As to the effect of iodin upon metamorphosis in salamanders, it is of no difference what concentration is used, iodin has no effect on development. Neither does it accelerate the growth of the legs, nor does it in the least stimulate metamorphosis. Since keeping the animals in weak solutions of iodothyrin results in almost immediate metamorphosis, it seems that iodin is not the chief factor that causes the specific action of the thyroid hormone; apparently the effect of iodin in tadpoles is merely due to some peculiarities of the frog larvæ as indicated above.

In conclusion it should be pointed out that thyroid substance may result in an acceleration of growth and development even in organisms that do not possess anything like a thyroid gland. Kunkel found that the larvæ of the common flesh fly develop more quickly if fed on thyroid substance and various observers (Shumway, Nowikoff) observed that in protozoa the rate of division can be increased markedly if thyroid substance is added to the culture medium.

The Relation of the Hypophysis Cerebri to Growth and Development

Aside from the thyroid gland the hypophysis cerebri is probably the most important endocrin gland in the control of the processes of growth and development. Since Pierre Marie discovered that in acromegaly the hypophysis shows important changes of its histological structure, attention has been called repeatedly to the growth controlling activity of the pituitary body. On the basis of our present knowledge it seems safe to say that the hypophysis elaborates a specific substance, which in some way as yet not well understood, accelerates growth, development of the sexual characters and, in certain groups of organisms, bodily development in general.

Introduction.—*Functions of Different Parts of the Hypophysis.*—Since the pituitary body is composed of several distinct portions the activities of which have early been recognized to be essentially different (Howell, Magnus and Schäfer) the question arose as to what part of the organ is involved in the control of growth and development. The feeding experiments (Schäfer, Smith (*c*) (*e*), Goetsch (*a*), Uhlenhuth's unpublished experiments) as well as the extirpation experiments show conclu-

sively that it is only the anterior lobe of the pituitary body which exercises a growth-controlling influence; and, according to Marinus, not the entire anterior lobe, but only the anterior lobe proper with exclusion of the pars tuberalis contains the growth-accelerating principle.

It was thought, at first, that the excessive growth in acromegaly is due to a destruction of the gland (Marie), and consequently the theory was developed that the hypophysis hormone inhibits excessive growth in the normal individual. Our present knowledge, however, contains ample evidence as to the contrary; the anterior lobe of the hypophysis manufactures a substance which stimulates growth and at least certain processes of development. Perhaps the most conclusive results, in this respect, have been obtained in the amphibians.

Relations in Lower Forms.—Even in the lowest organisms of the animal kingdom anterior lobe substance causes an acceleration of growth. Wulzen (*b*) has shown this to be the case in planarians, certain low worms. Several investigators (Nowikoff, Shumway, Chambers) studied the influence of pituitary extracts on the division rate of protozoa, but did not obtain conclusive results. Flather observed an increase in the rate of pulsation of the contractile vacuoles of infusorians kept in pituitary extract. It would be of great interest to know if plants are affected in their growth activities by pituitary gland, since this would throw light upon the question how far the effects of the active principle of the anterior lobe are due to the chemical structure of this substance and how far they are due to the specific structure of the organisms. Unfortunately only preliminary attempts have been made to determine the effect of the hypophysis substance in plants (Budington) and these have been negative.

Relations in Amphibia.—In 1914 Adler (*a*) removed the hypophysis from young larvæ of frogs and found that this resulted in a complete inhibition of development; the transformation of the hypophysectomized larvæ was suppressed. This result was confirmed by the more elaborate experiments of Smith and of Allen (*a*) (*b*), who found that in hypophysectomized frog larvæ first an inhibition of the development of the hind limbs is effected, while later on growth and development of the entire body is checked. The feeding of anterior lobe to tadpoles, in the experiments of Gudernatsch and Abderhalden, has not yielded conclusive results; but the more recent experiments carried out by Smith (*c*) (*e*) and by Hoskins (*c*) and Hoskins show that feeding of anterior lobe to the larvæ of frogs causes an acceleration of growth during the late larval period and a slightly precocious metamorphosis. Uhlenhuth has fed anterior lobe to salamanders; he was unable to demonstrate any influence during the larval period, but observed soon after metamorphosis an enormous acceleration of growth. The feeding was continued after metamorphosis and into the period of sexual maturity; this latter part of the experiment was of special interest, because the salamanders did not cease growing after they had reached

the normal maximum size of the species, but continued beyond it. Thus hypophyseal gigantism resulted as shown in Figs. 1 and 2.

Relations in Birds.—Only few experiments have been made on birds. Wulzen (*b*) showed that, if anterior lobe feeding is commenced in early

Fig. 1. Three male Ambystoma tigrinum; A and C fed anterior lobe of hypophysis, B control. The control animal B (approximately 185 mm. long) is the largest animal of this species ever reared in our laboratory; A (233 mm. long) and C (238 mm. long) are the largest hypophysis-fed animals. Note especially the elongation of the tail of the hypophysis-fed animals A and C. Reduced. Original.

life, growth of the chicks is maintained beyond the normal period, and giant growth may result in the male birds; while unfortunately only one single experiment is available to prove the latter effect, Wulzen observed

constantly a precocious commencement and an increased rate of crowing in anterior lobe-fed male birds. Clark claimed that anterior lobe feeding stimulates the egg laying in hens, but this assertion was disproved by Pearl and recently by Simpson.

Fig. 2. Two female Ambystoma opacum; A an anterior lobe-fed, B a control animal. A (130 mm.) is the largest hypophysis-fed animal, B is one of the largest animals reared in our laboratory (the largest animal reared in the laboratory was 113 mm., the largest animal among those caught in nature or found in museums was 117 mm. long). Reduced. Original.

Relations in Mammals.—Although numerous experiments were carried out on mammals, the results in this group of organisms are often contradictory and unreliable on account of the lack of proper controls and an insufficient number of experiments. Despite many negative experiments it seems, however, safe to say that also in mammals feeding of anterior lobe results in an increased rate of growth, and in precocious development, especially of the sex glands and secondary sex characters. Although ex-

periments yielding negative results are nearly as numerous as those that were positive, it appears that in most cases in which no acceleration of growth could be observed, either the period of growth was not long enough (Aldrich) or the accelerating influence was overlooked on account of the small difference it caused, or the doses employed were too small (Hoskins (*a*)). Robertson fed anterior lobe to white mice and observed a slight but constant acceleration in growth; he also reports that abnormally large mice may be obtained by stopping administration of the glandular substance at a certain period of life (see below). In rats several recent observers (Goetsch (*a*), Marinus, Klinger) found that feeding anterior lobe results in an increased rate of growth, and Goetsch (*a*) (whose experiments, however, appear to be very poorly checked and small in number) and Marinus observed precocious development of the sex glands accompanied by early development of the secondary sexual characters, libido, and potency, resulting in early and more frequent breeding. These experiments are supported by the results of the extirpation experiments. The partial extirpation of the anterior lobe (total extirpation is fatal) leads to a retardation of growth and an inhibition of the development of the sex glands accompanied by suppression of the secondary sex characters and failure of the libido and potency to develop, if extirpation is carried out in a prepubertal stage, while atrophy of primary and secondary sex characters accompanied by adiposity ensues after hypophysectomy in adult stages (Paulesco, Cushing (*b*) and his collaborators). Fully in accord with these observations are Exner's (*b*) experiments, according to which homoplastic transplantation of a sufficient number of anterior lobes to one individual results in 9 out of 11 rats in an increased rate of growth (see also Cushing).

Very little is known about the exact mechanism that underlies the growth-controlling and development-stimulating action of the anterior lobe of the hypophysis, although from the feeding experiments as well as from the study of the anatomical and histological structure of the gland it is to be regarded as certain that a hormone is elaborated in the anterior lobe, which passes into the circulation (Herring (*a*), Cushing and Goetsch). Robertson has even claimed to have isolated the growth-controlling principle (tethelin) from the anterior lobe, but it seems that the claim is based on rather inadequate grounds. Regarding the mechanism of the anterior lobe action the following facts are important.

Mechanism of Operation of Hypophyseal Factors.—Although in the main the anterior lobe substance stimulates growth and development in most organisms, there are considerable differences as to the details of the effects produced. These differences indicate clearly that a large part of the final effect is due to the specific reaction of a specific organic structure upon the active principle of anterior lobe hormone, a fact which is frequently neglected in the discussion of experiments on different species.

Even in the same individual the effect is different in different developmental stages. According to Robertson the anterior lobe substance when fed to mice exercises an accelerating effect upon growth only during certain periods of life, while in other periods growth may be even retarded; in the latter case the organism develops, as Robertson thinks, a compensatory mechanism and through the action of this mechanism, which persists even after the discontinuation of the hypophysis diet, abnormally large animals may be produced, if the hypophysis diet is discontinued at the proper period of growth. Similarly in the hypophysis fed larvæ of frogs Hoskins and Hoskins (*c*) found a retardation of growth in very young stages, which was sometimes so great that these larvæ remained permanently smaller than the controls, although larvæ treated with hypophysis at a more advanced stage grew larger than the controls. A retardation of growth in early stages was also found by Wulzen (*a*) and by Winternitz in hopophysis-fed chicks. Uhlenhuth saw neither an acceleration nor a retardation during the larval period of the tiger salamander, while after metamorphosis an enormously increased rate of growth resulted, if the hypophysis diet was continued. While in these cases no definite explanation is possible, some insight was recently gained into the causes which determine whether hyperpituitarism leads to gigantism or to acromegaly; it is now a generally accepted view supported especially by Cushing and his collaborators (but opposed by Falta) that hyperthyroidism leads to harmonious overgrowth of the entire body if it starts in young persons whose epiphyses are still open, while initiation of hyperpituitarism after the fusion of the epiphyses produces disproportionate growth of only the acra.

It is of considerable importance as regards the final result of anterior lobe administration whether or not the individual is in the possession of a normally functioning hypophysis; Smith (*c*) found that while normal tadpoles react with increased growth upon anterior lobe feeding, hypophysectomized tadpoles are able to utilize the hormone to a still greater extent and consequently their growth surpasses that of the normal hypophysis-fed animals. Well in accord with this experience is the important discovery made by Cushing that injection of anterior lobe extract, while it produces no effect in normal individuals, causes a rise in temperature of from 2° to 4° C. in hypophysectomized mammals; very likely both of these phenomena are brought about by the same mechanism.

Another noteworthy observation is that not all parts of the same organism react quantitatively in the same way to the anterior lobe substance. Hoskins and Hoskins (*c*), for instance, found that in tadpoles fed anterior lobe the tail grew more vigorously than the body. Uhlenhuth observed that in metamorphosed salamanders fed anterior lobe the tails attained such an enormous length that an entirely unproportionate appearance is peculiar to these animals (Fig. 1). It is, however, doubtful

that this phenomenon is identical as regards its causation, with the abnormal growth of the tail of anterior lobe-fed tadpoles. In salamanders (Ambystoma tigrinum) the male possesses normally a longer tail than the female; upon feeding hypophysis the tail-body ratio of the female is very little—if at all indeed—increased over the normal value; it is the male alone that shows the abnormal increase of this ratio. It is possible that in the salamanders the increase of the tail-body ratio is due to an increased function of the testes caused by the hypophysis diet. It is well to remember, in connection with these experiments, that one of the chief problems involved in the mechanism of the anterior lobe-action is how much of the effects described above is due to the direct influence of the anterior lobe substance and how much is due to changes of other endocrin glands caused by the anterior lobe hormone. In this respect the sex glands and the thyroid gland deserve special consideration.

Relation of Hypophysis to Sexual Development.—The experiments of Goetsch and of Marinus on feeding anterior lobe, the extirpation experiments of Cushing and of Bell and numerous clinical data (see Cushing and Falta) leave no doubt that the anterior lobe secretion if present in excess causes hyperplasia of the sex organs leading to precocious development of all sexual characters; in all probability Uhlenhuth's observations on the increased growth of the tail in salamanders is a similar case. The assumption of an intimate interaction between hypophysis and sex glands is supported also by the observation that pregnancy (Erdheim and Stumme) or gonadectomy (Hatai), the latter especially in males, result in an enlargement of the hypophysis and even in important histologial changes of the anterior lobe.

Interrelation of the Hypophysis and Thyroid.—That an interaction exists between the thyroid and the hypophysis has frequently been stated since Rogowitsch demonstrated considerable histological changes in the anterior lobe of the hypophysis of thyroidectomized rabbits. Rogowitsch himself declared these changes to indicate hyperactivity of the gland; the same view was taken later on by Stieda and, in regard to the posterior lobe, by Herring. Recently, however, Trautmann has studied the hypophyses of thyroidectomized goats and maintains that the weight determinations are of little value on account of the great variations of the weight of the hypophysis even under normal conditions and that the histological changes found in the anterior lobe of hypophysectomized goats are indicative of a degeneration (colloid degeneration of the "Hauptzellen" and replacement of functional elements by connective tissue). Similarly the thyroid has been found to undergo atrophy or retardation of further development after hypophysectomy (Adler (*a*), Rogers, Smith (*e*), Hoskins and Hoskins (*b*). From these observations an intimate interaction existing between hypophysis and thyroid seems evident. Experimental data suggest that even a vicarious function may exist between both

glands. Allen (*j*) found that hypophysectomized tadpoles, though they could not metamorphose if fed on normal food, would metamorphose upon administration of thyroid gland or even iodin, and Hoskins and Hoskins (*c*) recently demonstrated that thyroidectomized tadpoles at least begin to metamorphose upon administration of anterior lobe. Larson found that anterior lobe feeding in rats abolishes the effects of thyroidectomy. In his last publication Allen (*j*) suggests that at least in amphibians the pituitary gland may be necessary for the utilization of the iodin of the thyroid, and calls attention to the similarity of the functions of both glands in the amphibian organism. And indeed the rôle of the hypophysis in growth and development seems to have much in common with the action of the thyroid; in particular the lowering of the carbohydrate tolerance, and, in the absence of these glands, the lowering of the body temperature, the retardation of growth and the atrophy of the sex glands are effects common to both of them.

Relation of the Sex Glands to Growth and Development

One of the most important effects of the sex glands on growth and development is shown in the development of the secondary sex characters. The effects of castration have proved conclusively that these characters, at least in many animals, are dependent upon the presence of the gonads. The removal of the latter at an early (prepuberal) stage results in failure to develop the secondary sex characters. The fundamental changes following castration in man (Tandler and Grosz (*a*) (*b*) (*c*) (*d*)), in cattle (Sellheim (*b*) (*c*), Tandler and Keller), in deer (Röhrig), in guinea pigs and rats (Halban, Steinach, Marshall and Jolly, Hatai) afford sufficient proof of an intimate relationship between the sex glands and secondary sex characters. The removal of the sex glands before puberty causes the external genitalia to remain infantile and inhibits the development of the accessory reproductive organs, and of many external characters differentiating the male and female of the species. Similar relations exist among birds (Goodale, Morgan, Pézard), amphibians (Nussbaum, Harms, Bresca) and even among organisms as low as the crustaceans (Girard, Smith).

The sex glands control development, not by nervous connections, but by the elaboration of a specific internal secretion. If the mammary gland of a young rabbit is removed from its place and grafted to the ear of the same animal, it will develop like a normal gland, although its nervous connections have been severed. It may even form the structures of a secretive mammary gland and produce milk when the host becomes pregnant (Ribbert). Moreover, the regrafting of sex glands into castrated animals shows

that the presence of a functioning gonad, no matter where it has been grafted, prevents all the consequences of castration and results in normal development of the secondary sex characters, as shown by Marshall and Jolly, by Steinach, and by Moore in rats and guinea pigs, by Goodale, and by Pézard in birds (Fig. 3), by Nussbaum (1909), and Meisenheimer in

Fig. 3. Shows the effect of castration in the male domestic fowl. Five successive stages of the atrophy of the fleshy appendages of the head following castration. (After Pézard.)

frogs. The experiments by Nussbaum deserve special mention since this author prevented the implanted testes from forming any nervous connections. Probably the feeding or injection of sex glands has the same effect as transplantation (Pézard, though denied by Meisenheimer and Walker). Important evidence in favor of the hormonic action of the sex glands was furnished by Lillie, who discovered that in twins of different sex the sex characters of the female are more or less changed into male characters if the male hormones are permitted to reach the female through the circulation of the blood.

Not the entire sex gland but only the interstitial cells of the testicle

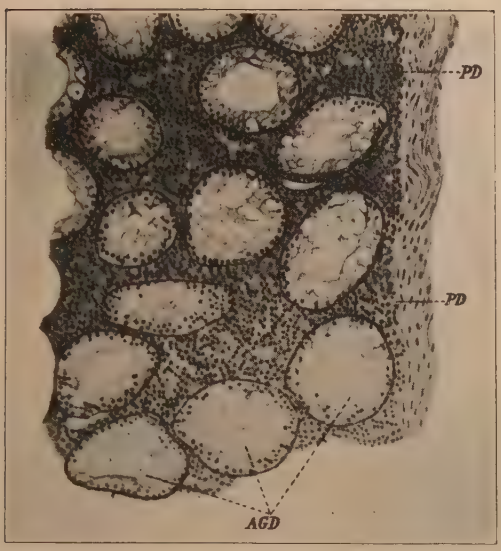

Fig. 4. Section through a guinea pig's testicle grafted (8 months before fixation) into the castrated male guinea pig and preventing the effects of castration. Demonstrates the endocrin function of the interstitial gland of the testicle. The generative part (seminal tubes) atrophied, the interstitial cells present and hypertrophied. After Steinach.

Fig. 5. Section through guinea pig's ovary treated with X-rays. Demonstrates the endocrin function of the interstitial gland of the ovary. The generative part (Graaffian follicles) atrophied, the interstitial cells (lutein cells) present and hypertrophied. After Steinach.

(Bouin and Ancel, Steinach) and the interstitial cells and *corpora lutea* of the ovary (Bouin and Ancel, Steinach) elaborate the sex hormones; the sex gland is differentiated into a generative and a glandular (interstitial gland) structure (Fig. 4 and Fig. 5).

The sex hormones are specific; the male hormone produces only the male, the female only the female characters, as demonstrated especially by Steinach's important experiments. Ovaries grafted into male rats castrated at an early stage produce only the female characters and may serve to suppress even such male characters as would develop after castra-

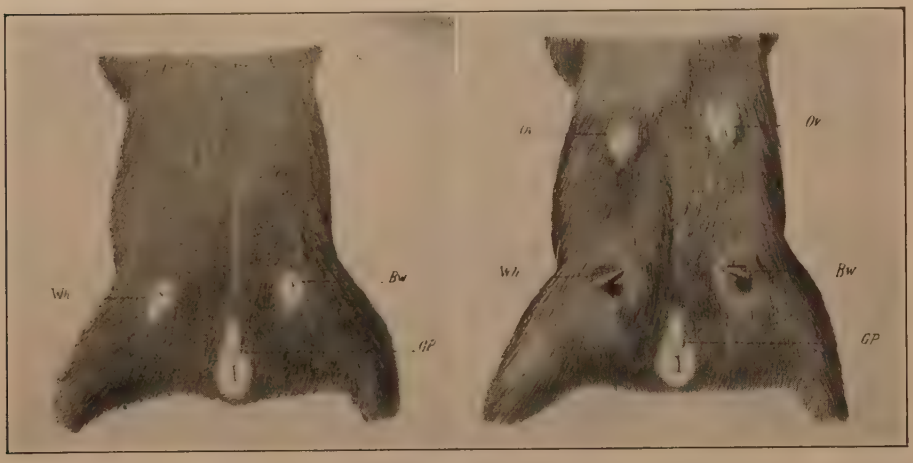

Fig. 6. A normal and a castrated male guinea pig; into the latter two ovaries were grafted subcutaneously (note the prominent areas on the abdomen) and caused feminization of the male (development of the female pregnancy type of the mammary gland). Demonstrates specific action of the female sex hormone. After Steinach.

tion (Fig. 6). The same fact is shown by Lillie's discoveries in the female free martin of cattle, which, through the action of the male hormones becomes changed in varying degrees into a male. In amphibians such specific action has been denied by Harms and by Meisenheimer, though, as it seems, on the basis of too small a number of experiments.

In mammals there exists an antagonism between the sex glands in that the presence of one may be destructive to the other (Steinach, Lillie), although for a short time both may exist in a functioning condition in the same individual, if the nutritional conditions are equally favorable to both (Steinach (*e*), Sand). This may result in the simultaneous development of male and female secondary sex characters in one individual.

Probably the sex hormones, like other hormones, are non-specific as regards the species from which they come. Pézard prevented the effects of castration in male domestic fowls by the injection of pig's testicle.

Notwithstanding this non-specificity we may expect that the action of the same sex hormone differs in different species. In no other instance are we so profoundly impressed with the importance of the condition of the particular organism as regards the final effect produced by the same agent. Two causes altering the susceptibility of the organisms toward the sex hormonic action deserve special mention, namely, hereditary sex determination and the age of the organism. There can be no doubt that the fertilized eggs of all species possesses a sexual predisposition; sex is inherited according to Mendel's law as shown by the sex ratio (Morgan (*a*)). The degree of this sexual predetermination, however, is different in different species. In mammals it seems to determine merely whether the developing embryo shall have a male or a female interstitial gland, while the further development, including that of the generative sex gands, is determined by the interstitial gland (Lillie). In insects, however, very little, if any, effect upon postembryonic development is left to sex hormones. In butterflies, primary as well as secondary sex characters are determined in the hatching caterpillar; castration or even implantation of the heterologous gland into the castrated caterpillar does not change the secondary sex characters of the individual (Meisenheimer, Kellog, Kopeĉ). There are, however, no good reasons to quote this instance as disproving the hormonic theory; we should not be surprised to find the absence of sex hormones in a group of organisms in which the entire system of internal secretions is present in an extremely rudimentary condition, or entirely absent. In crustaceans, at least the male characters seem to be controlled by sex hormones (Smith).

Since the number of sex characters increases with age, it is clear that the effect of administering or removing the sex hormones depends on the age of the individual. In mammalians and birds only slight changes are effected by castration in postpuberal life, while castration before puberty results in profound inhibition of the secondary sex characters. If development of the interstitial gland is prevented in embryonic life and the embryo is supplied with the hormones of the opposite sex, an almost complete change in the direction of the opposite sex may result (Lillie).

The effect of the sex hormones, in most species, seems to be the development of new morphological characters in both sexes. In such cases, as Tandler and Grosz pointed out in regard to man and other mammals, the removal of the sex hormones results in the maintenance of an infantile "neutral" type, but does not lead to the development of the characters of the opposite sex. In birds (Morgan (*b*) (*c*) (*d*), Goodale, Pézard) this is true only for the male hormone, which produces the fleshy appendages typical of the male, but otherwise leaves the species unchanged. The female hormone, however, has a suppressing action upon many of the neutral characters, in addition to its power of developing specific female characters (plumage, etc.).

There are two, as yet incompletely studied, phenomena which seem to contradict the conception of the hormonic development of the secondary sex characters; these are the occurrence of gynandromorphs in birds (Weber), in which one-half of the body is completely male, the other completely female, and Morpurgo's parabiotic rats. An incomplete knowledge of the conditions existing in these cases and a lack of space forbid discussion of their significance.

Little is known as to the mechanism of the action of the sex hormones, beyond the fact that they cause increased metabolism (Loewy and Richter). This agrees perhaps with Steinach's recent discoveries that the morphogenic effect of the sex hormones is quantitative; a mere hyperplasia of the interstitial gland of the ovary grafted into the castrated male leads to development beyond the female virgin characters and produces the structures characteristic of pregnant females.

Finally, it should be mentioned that removal of the sex glands results in overgrowth of the long bones. It is, however, doubtful whether or not the sex hormones possess a specific inhibitory action on growth. Facts are known which indicate hyperfunction of the pituitary gland after castration, especially in the male (see Hatai and under hypophysis). This finding in connection with the fact that castration delays closure of the epiphyses (Sellheim, Tandler and Grosz) may account for the overgrowth of castrated individuals.

Relations of the Thymus to Growth and Development

After Basch in 1903 had published his first accounts of a new method which permitted complete removal of the thymus gland from mammals, the view became widespread that the thymus plays an important rôle in growth and development. The numerous and elaborate publications by Basch, Klose and Klose's collaborators are responsible for this view. According to the experiments of these investigators, performed mostly on dogs, the following conditions may be observed, when the thymus is extirpated from dogs and other mammals a few weeks after birth. First, the growth of the animal as a whole is retarded; second, specific disturbances of the development of the skeleton result; third, development of the mental abilities is disturbed; fourth, hypertrophy of the sex glands is caused. Since Klose had found that these conditions develop only if the thymus is extirpated in very young animals, his results apparently received much support from the opinion that the thymus gland functions only during early postfetal development and atrophies after sexual maturity is reached. Hammar, however, has shown that this opinion is not correct; careful measurements of the thymus gland of healthy individuals of different ages demonstrated that the thymus gland persists after

sexual maturity and in man is found in a functional condition as late as 60 years or longer after birth. Klose had given especial weight to the changes of the bones which in the main were the effects of disturbed calcification due to lack of precipitated calcium in the body and were identified by Matti as rickets. Liesegang, one of Klose's collaborators, on the basis of these findings developed a theory of thymus function, according to which the thymus was considered the center of the nuclein synthesis; after removal of the thymus, in consequence of the disturbed nuclein synthesis, a phosphoric or nucleic acid acidosis develops in the organism, as Liesegang assumed, and by keeping the calcium dissolved prevents proper deposition of it in the bones. Dustin, who, upon embryological grounds, also holds the view that the thymus is the center of nuclein synthesis, recently has expressed himself more definitely as to the exact mechanism of the thymus function in growth and differentiation. Finding that a large thyroid always coincides with a small thymus and *vice versa* in the same individual, he thinks that growth is controlled by the thymus only indirectly by the aid of the thyroid, the latter organ being the cause of increased organic differentiation, tissue repairs, growth and development and mobilizing from the thymus the nuclein needed for these processes.

Well in accord with Klose's findings of a disturbed calcium metabolism, in the absence of the thymus, was an observation made by Soli; when he removed the thymus from hens, eggs were laid which did not possess a shell; upon feeding calcium to the thymectomized hens, the shells were again formed.

As to the rôle of the thymus in sexual development Paton, Adler (*b*) and Hewer believed that the thymus inhibits development of the testes, for Paton in guinea pigs and Adler in tadpoles had found that thymectomy results in an accelerated development of the testes as far as weight and size are concerned, and Miss Hewer found that feeding thymus retards the development of the testes. The results as to the rôle of the thymus in the development of the testes were, however, not uniform, for Soli published several articles in which he reported that thymectomy in cocks, guinea pigs and rabbits delayed the development of the testes.

The opinion that the thymus gland stimulates bodily growth received particularly effective support when Gudernatsch in 1912 and Romeis in 1913 began to publish their papers on the results of feeding thymus gland to the tadpoles of frogs and toads. If young tadpoles were fed on thymus, they began to grow more rapidly than the control larvæ and some of them reached enormous sizes. But while in these experiments the thymus favored growth, it frequently retarded or even inhibited completely the development of the larvæ. Since the same authors had observed that feeding thyroid to the tadpoles had just the opposite effect, it was believed from this time on that the function of the thymus is antagonistic to that

of the thyroid and that the thymus produces specific growth-promoting substances on the one hand and specific development-inhibiting substances on the other, the latter inhibiting the excessively rapid differentiation observed in thyroid-fed larvæ. Abderhalden has recently propounded the same view, though the evidence he could furnish in favor of it seems very unsatisfactory.

Lately very careful experiments have been carried out with a view to testing the validity of the conclusions derived from the older investigations. These experiments almost unanimously have brought to light facts demonstrating that the thymus gland does not control either growth or development. Nordman, who repeated the extirpation experiments on dogs, was the first to deny that extirpation of the thymus retards growth in a specific way or produces disturbances in the ossification of the bones. He considered that such effects were due, in the experiments carried out by previous authors, not to the lack of the thymus function in the thymectomized animals, but to crowded enclosures and insufficient food. Similarly, Pappenheimer, Hohnan and Marshall and Renton and Robertson could not observe any disturbance in growth and development after thymus removal. Recently Park and McClure published their very careful and critical experiments conducted on dogs and on a large scale; they show that normal growth takes place after thymus removal and prove that the development of the skeleton as well as of the testes of the thymectomized animals is normal. In amphibians (tadpoles), too, the removal of the thymus gland in early embryonic stages does not interfere with normal growth and development, at least during the larval period. (Adler (*b*), Allen (*e*).

Similar results were obtained in the feeding experiments. In 1916 Hoskins fed thymus to rats, but did not notice any effect on growth and development. Lately Uhlenhuth (*a*)(*b*)(*f*)(*g*) has carried out thymus feeding experiments in large numbers of the larvæ of salamanders. These experiments gave the following results: If small amounts of thymus are added to the diet the larvæ grow and develop at the same rate as the controls. If large amounts of thymus are added to the diet, metamorphosis is retarded *pari passu* with the amount of thymus administered. Not only development, however, is retarded, but also the rate of growth is slowed down. Animals that are fed thymus exclusively grow and develop only for a short time after hatching and finally growth as well as development becomes completely inhibited. Thymus does not contain either specific growth-promoting nor specific development-inhibiting substances; the inhibition of growth and development caused by pure thymus diet is a deficiency phenomenon and must be due to the fact that substances indispensable for the processes of growth and development are lacking in the thymus.

In protozoa, too, no effect in growth (rate of division) could be observed if thymus was added to the culture-medium (Shumway).

Thus the extirpation experiments as well as the feeding experiments point at present to the conclusion that the thymus gland does not produce any specific substances influencing growth or development. The feeding experiments have shown that certain specific substances needed for normal growth and development are absent from the thymus gland.

It seems, therefore, justified to assume that the thymus gland is not concerned in the control of growth and development.

SECTION II

The Thyroid Gland and Its Diseases

Anatomy, Embryology, Comparative Anatomy and Histology ..... *E. V. Cowdry*

Anatomy—Gross Morphology and Relations—Blood Supply—Lymphatics—Innervation—Embryology — Early Development — Cavitation — Colloid Formation—Ultimobranchial Bodies—Growth—Comparative Anatomy—Follicles—Interfollicular Epithelium—Other Interfollicular Cells—Colloid Morphology—Cytology—Reaction to Experimental Conditions—Interpretation of Appearances. (From the Anatomical Laboratory, Peking Union Medical College.)

The Thyroid Gland and its Diseases

Anatomy, Embryology, Comparative Anatomy and Histology

E. V. COWDRY

NEW YORK

Anatomy

Gross Morphology and Relations.—The thyroid gland is a reddish yellow, lobulated, U-shaped structure, divisible into right and left lateral lobes, which are joined together in the median line by an isthmus. It is named after the thyroid cartilage, so-called on account of its shield-like shape (Greek, *θυρεός*, shield, and *εἶδος*, form).

The thyroid is situated in the middle third of the neck and partially encloses the trachea dorsally (Fig. 1). Its ventral surface is covered by the infrahyoid muscles, the cervical fascia, and the skin. It is in relation dorsally with the first two to four rings of the trachea, the cricoid cartilage, esophagus, and pharynx, the common carotid arteries, vagus nerves, and other structures. It is held in place by a fairly strong capsule connected with the cervical fascia. This capsule is said to be divisible into two layers, an outer, which can be removed with ease, and an inner one, which is very adherent to the gland.

The isthmus is frequently absent, and even when it is present it is often difficult to palpate, owing to fibrosis. Occasionally in the normal condition even the gland itself cannot be felt at all. The right lobe is often a little larger than the left. The lobes measure about six centimeters in length. A so-called pyramidal process often extends cephalad from the isthmus, usually on the left side. It may even reach as far as the foramen cecum at the base of the tongue. It consists of typical thyroid tissue. In very rare cases it may be double, one on either side of the middle line. Accessory thyroids usually occur near the hyoid, but they may be found as far caudad as the bifurcation of the trachea. The weight of the gland is very variable, a good average being about 35 grams. Variations of as much as 20 grams are not to be considered abnormal. In some localities, depending upon altitude, climate, and other factors, it is normally larger than in others (Table 1). It is normally relatively one-fourth

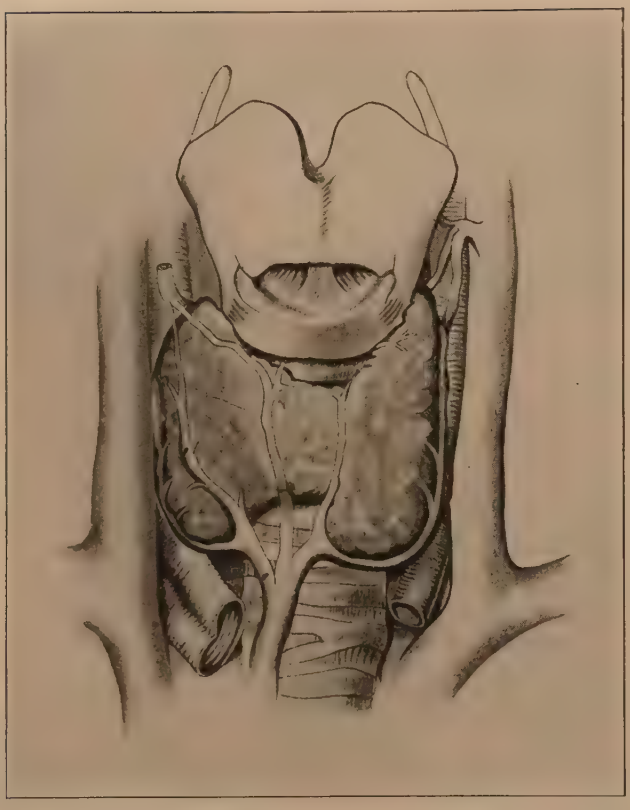

Fig. 1. Dissection of human thyroid gland, after Cunningham.

larger in women. There is often an increase in weight in menstruation and during pregnancy, which some consider to be due to hyperemia and others to increased colloid formation.

Variations.—

TABLE 1

VARIATIONS IN THE THYROID GLAND (AFTER WELLS, WITH ADDITIONS)

Type of Variation	*Observations*	*Reference*
Weight in United States	22 grams	Wells
" " Germany	30-60 grams	Virchow, Rauber
" " England	30-40 grams	Schäfer
" " France	22-24 grams	Poirier and Charpy
Absence of isthmus	15-20 per cent	McCarrison
" " "	10-15 per cent	Wells
Presence of pyramidal process..	60 per cent of 60 cases	Wells
" " " " ..	43 per cent of 60 cases	Marshall
" " " " ..	74 per cent of 147 cases	Zoja
" " " " ..	68 per cent of 153 cases	Streckeisen
Isthmus occurs as independent lobe	1 per cent	Wells

The variability of the thyroid gland is probably due to several factors. While it usually develops from a single median ventral outpouching of the pharyngeal epithelium, the contributions from the fifth branchial clefts, common in lower forms, may persist to some extent in man, giving rise to various rudimentary structures (see p. 211). From the standpoint of its origin, therefore, there are three potential variables, the median and the two ancestral lateral anlagen. The great changes in position, with the development of the organs of the neck and thorax, introduce a second opportunity for variation through incomplete or excessive caudad migration. And finally, the absence of a duct anchoring the gland, as it were, to the alimentary canal, combined with the fact that the tissue can function equally well in almost any part of the neck region, favors the persistence of variations.

Blood Supply.—The blood supply is very rich. The superior thyroid arteries arising from the external carotids run to the apex of each lateral lobe and give off numerous branches, which ramify over the ventral and medial surfaces and penetrate into the substance of the gland. They sometimes unite at the isthmus. Usually a dorsal branch anastomoses with a twig from the inferior thyroid artery of the same side. Apparently the anastomoses take place on the surface of the gland only. The inferior thyroid arteries are as large or larger than the superior thyroids. They spring from the subclavians and runs on the lateral surfaces of the gland. They are intimately related to both the superior and inferior parathyroid glands. Very frequently there is also a thyroidea ima artery, which arises from the arch of the aorta and runs to the isthmus.

The blood leaves the thyroid through numerous veins which form a dense plexus beneath the capsule. The superior thyroid veins are the most constant. They leave the ventromesial surfaces of the lobes and open into the facial or internal jugular veins. The middle thyroid veins run laterally to enter the jugulars. They frequently anastomose with the pharyngeal venous plexus. The inferior thyroid veins leave the caudad aspect of the gland, and after forming a plexus on the ventral surface of the trachea, pour into the left innominate vein. A thyroidea ima vein, usually discharging also into the left innominate, may occur. All the veins are said to be devoid of valves.

Lymphatics.—The lymphatics arise in networks about the follicles and run along with the connective tissue septa to the surface of the gland, where they form a very rich subcapsular plexus. While the chief drainage is to the deep cervical lymph glands, it may pass in almost any direction, cephalad to the prelaryngeal nodes or caudad to the pretracheal ones. Major has described, in the dog, the direct passage of one lymphatic trunk into the left subclavian vein, but it is not known whether this ever occurs in man.

Innervation.—The nerve supply of the thyroid has been the subject of much controversy. It is certainly for the most part sympathetic. The main points are illustrated in Fig. 2. Preganglionic visceral motor fibers from the upper thoracic nerves enter into the superior and middle cervical sympathetic ganglia, where they arborize about sympathetic cells, giving rise to postganglionic fibers which are unmyelinated. These pass

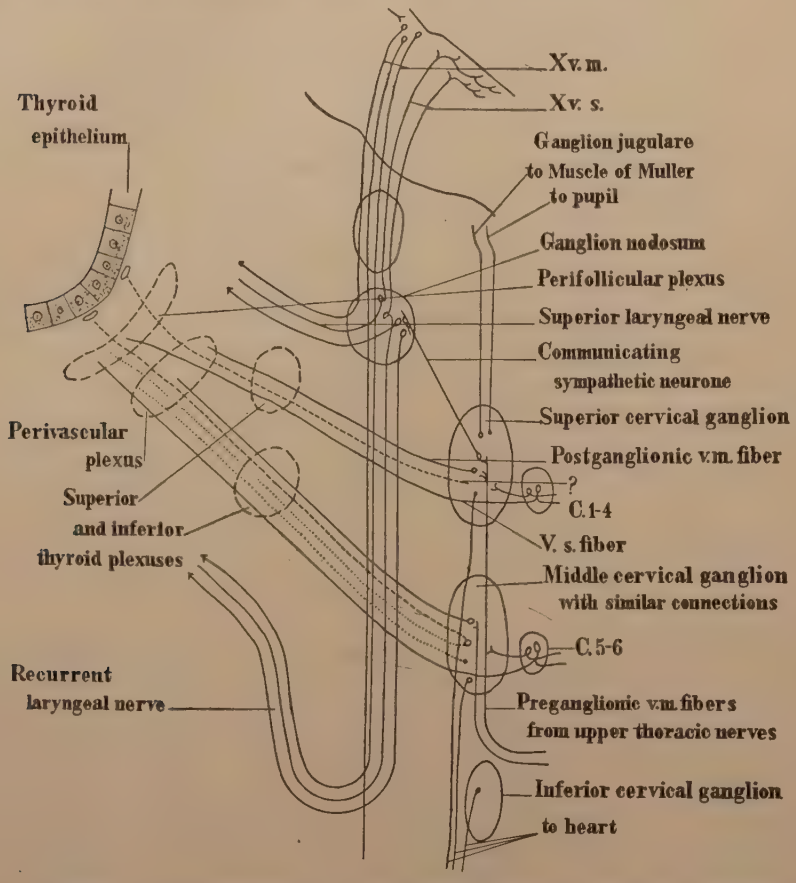

Fig. 2. Scheme of the innervation of the thyroid gland. Doubtful connections are dotted. *v.m.* visceral motor and *v.s.* visceral sensory.

in the direction of the gland, and contribute to the formation of the superior and inferior thyroid plexuses about the thyroid vessels. Whether fibers from other sources of the same or different nature also enter these plexuses, we do not know. The fibers follow the divisions of the respective arteries along the connective tissue trabeculæ into the gland, and give rise to very rich perivascular plexuses in the interfollicular connective tissue. Here the vasomotor postganglionic fibers terminate in association with the blood vessels.

Dense perifollicular plexuses are also found enclosing the thyroid follicles. Fine twigs from such a plexus terminate in little knob-like swellings at the bases of the gland cells, the function of which has not yet been definitely ascertained. Cannon and Cattell conclude, as a result of their studies of the electromotive phenomena accompanying secretion, that these terminals belong to secretory sympathetic fibers. Cannon, Binger and Fitz, and Cannon and Fitz present additional evidence in support of the same contention. They anastomosed the anterior root of the phrenic with the cervical sympathetic trunk, and claimed that symptoms of hyperthyroidism were thus produced by the repeated stimulation of the gland through the phrenic and sympathetic at each respiration. The frequent association of lesions in the superior cervical sympathetic ganglia with exophthalmic goiter, as described by Wilson and others, is of interest also in this connection.

Mott has, likewise, described chromatolytic changes in all the cells of the central nervous system in hypothyroidism; and Wiener observed the atrophy of a lobe of the thyroid, and a decrease in thyroglobulin on the side from which he had removed the inferior cervical ganglion (citation from Schafer). Yet it is claimed that thyroid grafts are in no way dependent upon nerve supply in order to produce secretion (Kummer).

From the anatomical point of view, these fibers terminating in contact with the secreting cells may equally well be visceral sensory; but we would hesitate to suggest that this is the correct interpretation. Visceral sensory fibers for the thyroid gland do arise from the cells of the first six cervical spinal ganglia, but their peripheral relations are unknown. Very little reliance can be placed in isolated descriptions of nerve cells occurring in the interfollicular connective tissue. There is no anatomical evidence in favor of the existence of sympathetic reflexes, as postulated by same authors.

In addition to this sympathetic connection, fibers of the superior and recurrent laryngeal nerves have been described entering the gland. The recurrent nerves are thought to carry vasodilator fibers. Ossokin has obtained evidence indicating that the inferior laryngeal and the pharyngeal branches of the vagus both supply twigs to the gland. Ascher concludes that secretory or excitoglandular fibers are contained in the superior and inferior laryngeal nerves, but the criteria which he used for secretory activity are not entirely satisfactory. Gley writes that "it has been thought possible to prove directly the action of the nervous system on the thyroid by showing that stimulation of the laryngeal nerves (L. Ascher and M. Flack, 1910) increases the excitability of the depressor: it being admitted, following the researches of E. de Cyon, that the latter is dependent on the thyroid secretion." This dependence, however, is denied by Schafer. The difficulty of maintaining functioning grafts of

the thyroid may be due to the lack of nervous influence, though this is denied by Kummer.

Embryology

It would seem, from the recent work of Norris (*b*), that the conflicting statements with regard to the normal mode of development of the thyroid gland are merely expressions of the wide latitude of variation.

The thyroid gland begins to develop very early (embryos of about one millimeter and a half) as a median evagination of the endoderm of the floor of the pharynx between the first and second pair of pharyngeal pouches (see Figures 2 and 3 of section on Parathyroids), there being no regular contributions from the lateral branchial clefts, as was formerly supposed.

Early Development.—At this stage considerable variation becomes apparent, and Norris illustrates his account by means of the accompanying diagram (Fig. 3). Development may take place in three directions: the downgrowth may be solid (c), or possess a hollow stalk (d), or be double (e). The last named condition is rare, and Norris says that it "would seem to support" Patten's idea that the thyroid may be the representative of two separate glands associated with the pharynx in certain lower forms.

The stalks connecting the glands with the pharynx now elongate, so that the conditions represented in (g), (h) and (i) are brought about.

With complete separation from the pharynx, in embryos of from about four to seven millimeters, a number of variations arise, as is illustrated in diagrams (j) to (q). Division may occur near the pharynx, leaving a large amount of the tissue of the stalk in association with the thyroid body, thus favoring the formation of a pyramidal lobe or thyroglossal duct; and, conversely, the development of "lingual rests" and "suprahyoid bodies" results when separation takes place near the body of the thyroid, leaving a larger amount of tissue in association with the pharynx.

Cavitation.—The next change consists in the formation of closed cavities within the gland mass (r), which, according to Norris, are quite independent of the original lumen of the thyroid pouch. He attributes considerable importance to these intraglandular spaces, because he has also found them in approximately the same stage of development in representatives of several classes of animals. These spaces finally open to the periphery of the gland anlage (s), and the definitive follicular cavities begin to appear in their walls (t).

Colloid Formation.—It is not until after birth that any considerable amount of colloid material is formed within the follicles, and iodin may

be detected chemically in the gland. According to Kummer, the iodin increases in amount to thirty years of age and decreases after forty. It is to be noted that the colloid in the hypophysis is also a very late development.

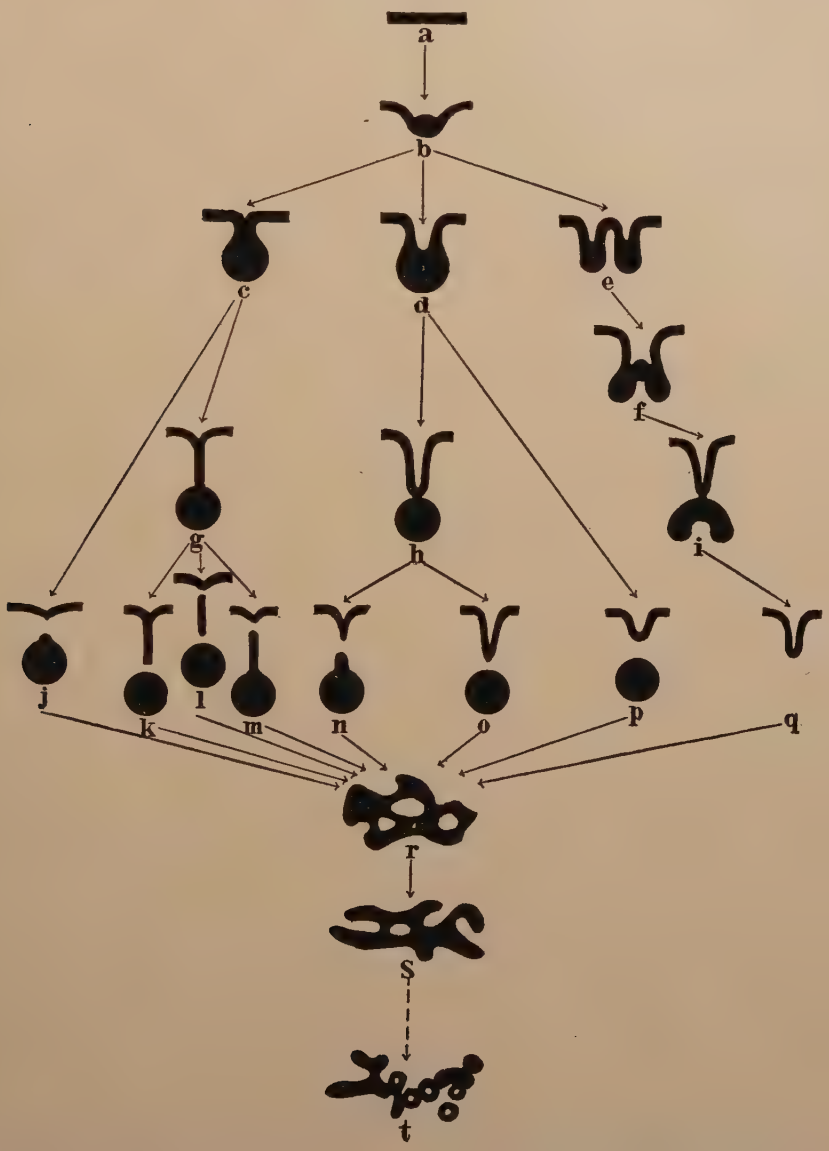

Fig. 3. Scheme of the development of the human thyroid gland, after Norris.

Ultimobranchial Bodies.—In young embryos certain structures arise from the fifth or last gill pouches, called for this reason "ultimobranchial bodies," which constitute in part the lateral thyroids of lower forms.

In fishes they form an organ called the suprapericardial body. They are to be regarded merely as rudiments in man and usually do not persist at all in the adult, though they have occasionally been found in close association with the parathyroid glands. Schilder and Erdheim believe that they form true thyroid tissue in cases of thyro-aplasia. In thyro-aplasia it would appear that the parathyroids are often present and normal, though Siegert and others have recorded their absence. Nickerson has described the replacement of the lost thyroid tissue by thymus in a calf.

Growth.—The thyroid gland, according to Jackson (*a*), "increases slowly but steadily in relative size during the prenatal period." At birth it averages about 0.125 per cent of the total body weight. Numerous observations have been made on the subsequent growth of the thyroid in man, but they are scattered and uncorrelated. The white rat is the only animal whose growth phenomena are being standardized, chiefly through the researches of Donaldson and his associates at the Wistar Institute. Jackson finds that the thyroid attains its greatest relative size at birth, and then progressively decreases relative to body weight, though, of course, its absolute weight increases. Hatai and Jackson agree that in the rat there are no differences in weight of the thyroid between the two sexes; this is an interesting observation when we remember that in man the organ is generally thought to be relatively heavier in the female. A comparison of the laws of growth in the rat and man has been made by Donaldson, and it would seem that there are many points of similarity. Since the weight of the gland is so dependent upon the amount of stored colloid, there is always this element of error in comparisons by weight or volume with other ductless glands. The method advised by Bensley for estimaitng the relative amounts of parenchyma and colloid is laborious, but gives valuable information. He photographs sections and makes tracings on cardboard of the contained colloid and parenchyma, cuts them out and weighs them, and thus obtains a ratio.

Some idea of the growth energy possessed by the thyroid gland is given by Jackson's experiments of holding young white rats at maintenance of body weight for several weeks by underfeeding. It was found that this treatment produced a well defined loss in weight in the thyroids, as compared with the hypophysis and suprarenals, which showed a considerable increase. Similarly, castration brings about a reduction in the rate of growth of the thyroid and an increase in that of the suprarenals and hypophysis (Schafer), from which we would likewise conclude that the growth energy of the thyroids is relatively small. As age advances retrogressive changes normally occur in the gland, characterized by a relative increase in the connective tissue at the expense of the secretory epithelium.

Comparative Anatomy

The thyroid gland is unknown in invertebrates, and becomes more and more highly developed the higher we go up the vertebrate scale. Its primitive connection with the pharynx is maintained through the ammocete stage of the development of the lamprey. Its homology with the endostyle of tunicates is uncertain. In most fishes it consists of very small groups of follicles scattered along the ventral aorta. In amphibia, birds, and reptiles it is more condensed. The bilobed condition in man is characteristic of mammals generally. Kummer states that "the iodin content depends also upon the species of animal. The herbivora show a maximum, the carnivora a minimum, and the omnivora an average amount of iodin."

These chemical analyses, together with the difference in the susceptibility of different animals to thyroid and parathyroid extirpation, lead one to believe that the glands are specifically adapted to meet the particular needs of different groups of animals. An extension of the statistical methods, which are bringing out such interesting points in normal development, to the phylogenetic series in the investigation of all the endocrin organs, is greatly needed.

Follicles.—The thyroid gland is made up of a mass of closed follicles containing a viscid material called "colloid." The follicles vary greatly in size and in shape. Sometimes they are very tiny and present little or no lumen, while in other cases they may normally attain a diameter of several hundred microns. Their shape is largely dependent upon intraglandular pressure. Saccular and tubular forms are of quite frequent occurrence, in addition to the more or less spherical vesicles which predominate. The follicles are embedded in loose areolar and elastic connective tissue, and the whole gland is surrounded by a fairly dense capsule (Fig. 4).

Interfollicular Epithelium.—Embedded in this connective tissue between the follicles, we occasionally find small irregular clumps of distinctly epithelial cells. These intervesicular or interfollicular cells, as they are called, are known to vary greatly in number at different ages, though their history has not been carefully worked out in any form. They are very numerous before birth and seem to decrease progressively as age advances. In the normal adult they are fairly abundant. According to Wilson, they become rearranged into secreting follicles in cases of exophthalmic goiter. Many investigators, therefore, regard them as persistent embryonic cells, possessing the power of differentiation into secretory epithelium as the demand arises. Bozzi, however, could detect no changes in these cells after removal of large parts of the gland, suggesting perhaps, that after all they may not possess secretory potencies (citation from

Wells (*b*)). Under certain conditions they are said to give rise to adenomata. According to Vincent (*a*) and others, they resemble closely the cells of the parathyroid glands, and it is claimed that they increase in number after parathyroidectomy; but as yet no detailed comparison has been made with the aid of methods adapted to the demonstration of mitochondria and other details of cytoplasmic structure. Pending further information, it is, therefore, unsafe to base generalizations upon this questionable analogy. Certain it is that these cells and those of the parathyroids develop from different embryonic anlagen.

Fig. 4. Section of human thyroid gland with rather lobulated follicles completely filled with optically homogeneous colloid substance. Note the desquamation of cells into the follicular cavity (magnification 900).

Other Interfollicular Cells.—Small clusters of lymphocytes and even fragments of thymus IV (see section on Parathyroids) are quite often found in the intervesicular tissue; the latter usually in association with the glandulæ parathyroideæ IV. Small cavities, lined with ciliated epithelium, occasionally occur also in the same location.

Colloid Morphology.—The colloid material is stored within the follicles. As seen in fresh preparations it is a clear viscid substance. In well fixed tissues it stains strongly with eosin and occupies the entire vesicular cavity. It is said that a small fraction of it is basophilic (see p. 215). In sections it frequently presents a vacuolated appearance indicative, perhaps, of variations in density or of droplets of other material. Jackson describes the production of these vacuoles through the solution of

desquamated epithelial cells. Their remarkably close correspondence with the individual vesicular cells (Fig. 5) indicates that, in some cases at least, they are produced by the cells and represent a more fluid secretion. The irregular notched border of the colloid substance, which is frequently met with, is probably due to the shrinkage caused by fixation. Newly secreted colloid is more fluid and stains less intensely than that of longer standing, though some believe the reverse to be true. According to Gley, "pilocarpin causes swelling of the thyroid and the collection of colloid matter in the vesicles." It is also claimed (Licini) that the colloid is increased by removal of the pancreas, as well as by thyroid feeding.

Fig. 5. Portion of wall of human thyroid vesicle showing close association of clear droplets with individual cells (magnification 900).

It is generally admitted that the colloid cells of Langendorff, which are sometimes present, are undergoing degeneration, being in the last stages of cytomorphosis. The presence of two distinct cell types, as discovered by Bensley in the opossum and illustrated in Fig. 6, is interesting, since it indicates the possibility of a plural secretion.

Iodin Content of Colloid.—The chief characteristic of the colloid substance is its iodin content, which varies in amount with sex, season, age, and diet (McCarrison (*b*)). Baumann's claim that giving foods rich in iodin increases the percentage of iodin in the gland, remains unconfirmed (Gley). In certain intoxications colloid with different staining reactions has been described. Vincent claims that "iodin is absent from the thyroids of some animals" and that it cannot always be found in the human thyroid, and Schafer seems to think that the autocoid is not necessarily iodin containing. More recently, however, Kendall has isolated from the thyroid a crystalline substance containing iodin, which possesses most striking physiological properties.

Colloid Resorption.—Champy's experiments with tissue cultures of the thyroid are of interest with regard to the normal mode of resorption of the colloid. In his experiments he finds that it passes through the follicular epithelial cells into the neighboring lymphatic spaces. Since the resorption is nearly complete in twenty-four hours, he concludes that it normally takes place quite rapidly in the organism. In his opinion, the contents of the follicles are almost completely renewed every twenty-

four to thirty-six hours. We have no evidence whatever from other sources bearing on this important point.

Cells in Colloid.—The presence of a few desquamated epithelial cells in the colloid substance within the follicles can hardly be regarded as abnormal. When, however, it is very marked, care must be taken to exclude the possibility of post-mortem change. We occasionally find in the colloid substance erythrocytes and pigment produced through their disintegration.

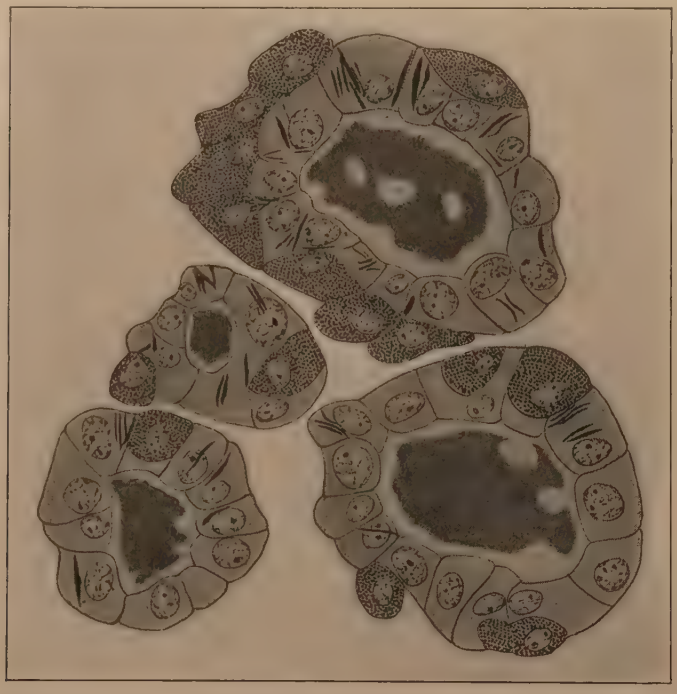

Fig. 6. Section of an opossum's thyroid showing two types of cells and intracellular crystalloids, after Bensley.

In the living state, teased out in salt solution, the secretory cells present a fairly uniform appearance in man.

Cytology.—Each cell contains a spherical nucleus with prominent nucleoli. In the cytoplasm droplets of colloid and occasionally of fat may be seen. The mitochondria are hard to distinguish, unless a little janus green is added to the solution; this quickly stains them a bright bluish green.

Mitochondria.—Under normal conditions the mitochondria occur in the form of filaments about 0.2 μ in diameter and varying in length from 0.2 to 4.0 μ. They are usually disposed parallel to the long axis of the cell, and are most abundant in the distal zone of the cell, next to the

lumen and remote from the basement membrane. Goetsch (*a*) has found that they constitute a valuable criterion of the activity of the epithelium.

Cell Inclusions.—Glycogen and crystalloids are of comparatively rare occurrence, but when they do occur they can be easily studied in the fresh condition. It may be remarked that the crystalloids sometimes resemble quite closely those occurring in the interstitial cells of the testis. Both fat and glycogen are said, as is the case in most tissues, to be more abundant in old subjects. Cells undergoing mitotic division are rare.

Reticular Apparatus.—By appropriate methods of fixation and staining rather more can be made out of the intimate structure of the cells. Using Golgi's arsenious acid method, Negri has described the presence of a well formed reticular apparatus in these cells, in the form of a circumscribed network which blackens with silver. It is located between the nucleus and the lumen of the follicle. I have confirmed and extended Negri's observations by using Cajal's latest uranium and silver nitrate method, which gives preparations as illustrated in Fig. 7. Unfortunately, the evidence is not conclusive that a similar network occurs in the living condition, so that we are unable as yet to interpret these findings. If it does occur, and if Bensley's hypothesis is correct, that it is the homologue in the animal cell of the vacuole in plant cells, its study should afford valuable information with respect to the condition of the epithelium. Iron hematoxylin preparations show that the centrosome is located in the distal pole of the cell, that is to say, in that part of the cell remote from the basement membrane and near to the lumen. Secretion antecedents within the cells have been discovered by Bensley (*b*) through the elaboration of a new method of technic, consisting of fixation in formalin-Zenker and of staining with Brazilin and water blue. They are seen in the form of vacuoles, which occur exclusively in the proximal part of the cell near the perifollicular blood vessels. The vacuoles contain a dilute solution similar in its properties to the intrafollicular colloid. This discovery may go far toward clarifying our whole conception of the structure of the thyroid gland.

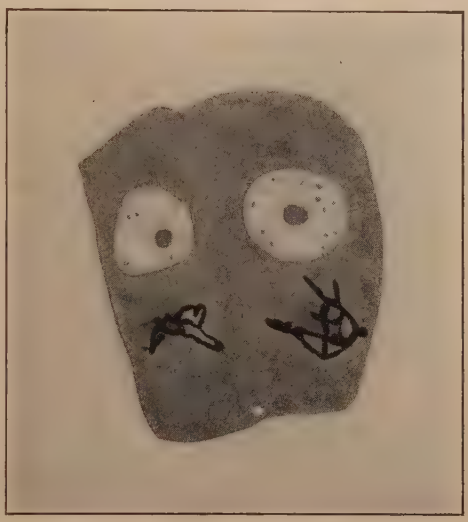

Fig. 7. Section of a pigeon's thyroid prepared by Cajal's uranium and silver nitrate method in order to demonstrate the reticular apparatus which is here seen in the form of a blackened network between the nuclei and follicular lumen.

Secretory Phenomena.—Cell Polarity and Mode of Secretion.—Bensley (*b*) has advanced the following hypothesis as to the mode of secretion. He claims that the original polarity of the thyroid cell has been reversed, so that it now secretes in the direction of the perifollicular blood vessels, and not invariably into the lumen of the follicle, as has been generally supposed. He compares it with an acinus cell of the pancreas, which possesses ordinary proximodistal polarity, substances passing from the blood stream (B. V.) through the basement membrane into the cell and through it in a distal direction toward the duct, as is illustrated by the direction of the arrow in Fig. 8A. In the thyroid cell, on the

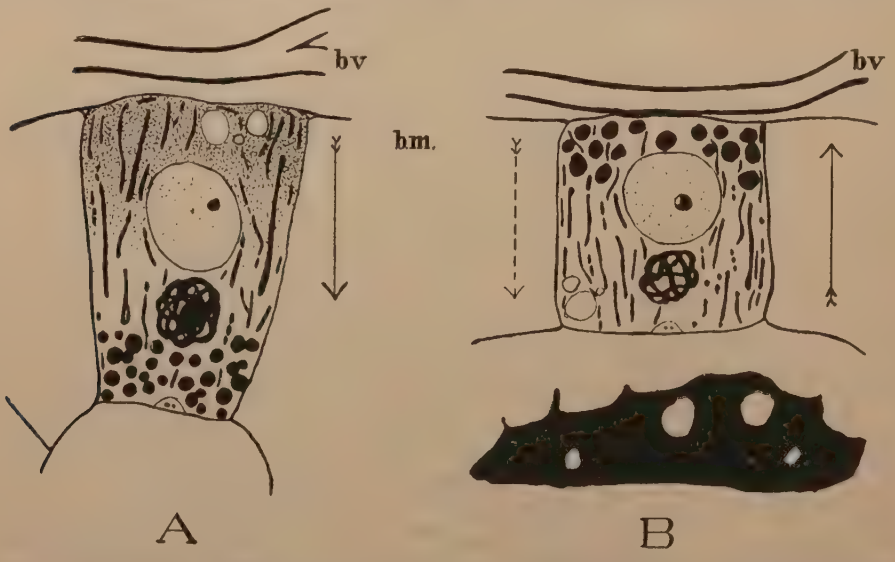

Fig. 8. Diagram illustrating the polarity of an acinus cell of the pancreas (A) as compared with a cell of the thyroid epithelium (B).

other hand (Fig. 8B), the condition is reversed, the materials passing from the blood stream (B. V.) into the cell, then out of the cell again and back into the blood stream, as is also indicated by the arrow. As structural evidence of this reversal in polarity, he cites the location of the secretion antecedents next the basement membrane, just as in the pancreas the zymogen granules are heaped up near the lumen of the duct; and the presence of fat droplets at the opposite end of the cell, as in the pancreas. His contention is also supported by convincing experimental evidence.

Colloid Formation and Resorption.—In explanation of the occurrence of intrafollicular colloid, he suggests that, when the rate of secretion is in excess of the demand, it is passed in the reverse direction into the follicular cavity. He writes: "According to this conception of thyroid secretion, the colloid in the thyroid vesicles is *per se* no measure of the activity of the gland at the moment of observation, though its consistence

and its qualities may offer valuable indications of the capacity of the thyroid cell for normal storage. The colloid in fact may be the product of a storage phase, which preceded the examination of the gland by a considerable period of time, since it is necessary to explain the resorption of this material only under the conditions where the normal secretory activity of the gland is insufficient to meet the functional demands. Accordingly, also, lack of colloid in the gland does not necessarily mean depression of the gland activity below the normal rate at the time of observation, though it probably does mean there is such a depression of physiological efficiency, or has been at some previous period, and either that the gland has not risen above the level of secretory rate needed for direct export, or that there has been a failure of the normal mechanism of regulation."

Embryologic Evidence of Primitive Secretory Ducts.—Bensley's view that the secretion is poured directly into the blood vessels and lymphatics is strongly supported, up to a certain point, by Norris's embryological studies, to which reference has already been made. According to these studies the intraglandular spaces, which he has found in the developing gland, represent ancestral lumina. These communicate with the periphery of the gland anlage in the course of development, and become invaded with connective tissue, blood vessels, and lymphatics. The follicles develop through the formation of cavities in their walls, which are lined by a single layer of cells. He, therefore, suggests that the perifollicular spaces in the mature gland represent the ancestral lumina, and that one would naturally expect the secretion to be directly poured into them; hence it may be unnecessary, as Bensley has done, to postulate a reversal in polarity.

Very recently, however, I have found that the reticular apparatus moves actively from one pole of the thyroid cell to the other under quite normal conditions which I believe to be the visible expression of changes in the direction of secretion. As has already been mentioned it generally occurs in the distal part of the cell between the nucleus and the follicular cavity (Fig. 7). Its distance from the lumen is usually about the same in individual follicles. Occasionally the position is completely reversed so that it is found on the other side of the nucleus. This reversal may occur sharply in one cell only, or a cross section of a follicle may show successive stages in proximal migration. Migration may also take place in the opposite direction, all the reticular material moving toward the follicular cavity. These changes seem to be more frequent when the epithelium is high and columnar and the cells are perhaps more active. An examination of other glands indicates some correlation between the position of the reticular apparatus and secretory polarity. When the secretion has definite direction it is indicated by the position of the reticular apparatus between the nucleus and the discharging pole of the cell (acinar,

gastric and salivary glands); when it merely seeps through into the tissue spaces, veins or lymphatics, as the case may be, the position of the reticular apparatus is highly variable (islet cells and anterior lobe cells of hypophysis); and, finally, when its position becomes reversed, as it often does in the thyroid, we naturally look for a reversal (probably temporary) in the direction of secretion.

At present we have no conclusive anatomical evidence bearing upon the question of whether the secretion is continuous or intermittent. We may say, however, that in none of the endocrin organs do we see indications of well marked periodicity, as is the case in certain of the cells of the stomach and other glands pouring their secretion into the alimentary tract.

Reaction to Experimental Conditions.—The structure of the thyroid epithelium is easily modified experimentally, but the changes are difficult to control and interpret. We have good reason to believe that it is affected (1) by variations in diet, (2) by the activity of other endocrin organs, (3) by inanition, (4) by variations in temperature, and (5) by unhygienic conditions, as well as by medication; and we strongly suspect that many other factors are involved.

Diet.—In connection with diet, Bensley (*c*) has found the opossum very well suited to experimentation, because, when this animal is kept in captivity, the thyroid undergoes a very marked hyperplasia, which he has found to be characterized "by disappearance of the stored colloid and of the intracellular crystals, and by the appearance in the free ends of the epithelial cells of granules," which he interprets as a new secretion antecedent (see p. 217). He experimented with various diets and with iodin administration. With an unrestricted diet the hyperplasia was very great and was not inhibited by dosage with iodin. When, however, the animals were allowed just sufficient food to maintain body weight, no traces of hyperplasia could be seen. Apparently, therefore, the hyperplasia "can be controlled by diet alone," even when refractory to iodin. He then attempted to ascertain the particular food constituent in the unrestricted diet responsible for the production of hyperplasia, and obtained results suggestive of the protein fraction, which have since been confirmed by Burget.

Gland Feeding.—Kojima finds that feeding thyroid, in the rat, has much the same effect as iodin administration, causing a flattening of the thyroid and an increase in size of the parathyroid cells, while administration of the extract of the posterior lobe of the hypophysis, or of adrenalin, brings about an enlargement of both. According to Wilson and Kendall, structural changes are always accompanied by variations in iodin content.

Temperature.—Mills believes that variations in external temperature exercise a marked effect upon the structure of the gland. He experimented on dogs, cats, guinea pigs, and rabbits, and found that "animals

kept at 30° to 37° C. for several days showed the following changes in almost every case: The colloid content of the vesicles was increased in amount, presented a uniform appearance, and stained rather intensely with eosin; epithelial cells lining the vesicles were decreased in height, often entirely flattened, their cytoplasm and nuclei appearing rather compact and dense. That is to say, the thyroid had an inactive appearance. On the other hand, in animals subjected to low out-of-doors winter temperature, for the same period of time, the colloid material was diminished in amount and the epithelial cells became quite columnar, suggestive of the appearances which we are accustomed to associate with hyperthyroidism. The same author has described variations in the gland after the administration of morphin and quinin.

Hygiene.—According to Burget, unhygienic conditions alone are sufficient to bring about hyperplasia, which is a partial confirmation of McCarrison's observations.

Inanition.—Jackson (*b*) has found that the thyroid responds very quickly to inanition, and suggests that some of the structural changes following different diets may be due merely to their varying food values.

Interpretation of Appearances.—There are many confusing sources of error in interpreting the histological appearances as we find them. In the first place, the range of normal variation has not yet been established for a single species. Regional variation must also be reckoned with, for specimens taken from different parts of the same apparently normal gland often present a very different appearance. It is for this reason that serial sections are so useful in the study of small glands in experimental series. Moreover, the thyroid gland undergoes autolytic changes with extreme rapidity, so that the specimens should be taken as soon after death as possible. Mechanical injury with the forceps and the drying of a surface film of tissue before fixation must also be avoided. Cutting with scissors is faulty technic, because of the pressure exerted on the tissues. Specimens kept in salt solution at body temperature are ruined, because autolysis is accelerated. The penetrating power of the fixative must also be considered and due allowance must be made.

The problem of finding reliable histological criteria of secretory activity is indeed a difficult one. Our older methods, rigorously controlled, should be used hand in hand with the newer technic. Of the cytoplasmic constituents recently discovered, the mitochondria alone have proved of service in the investigation of human material. In experimental studies the reticular apparatus and the secretion antecedents of Bensley deserve more attention.

The Physiology and the Experimental Pathology of the Thyroid Gland . . . . . *Swale Vincent*

Introduction—Earlier Theories as to Function—Extirpation Experiments upon Animals—The Internal Secretion and Its Nervous Mechanism—The Nature of the Substance Secreted and Its Physiological Actions—The Influence of the Thyroid upon Metabolism—Thyroid Transplantation—The Relation to the Sexual Functions—The Relationship between Thyroid and Parathyroid—Summary.

The Thyroid Gland and Its Diseases

Physiology, Physiological Chemistry and Experimental Pathology

The Physiology and the Experimental Pathology of the Thyroid Gland

SWALE VINCENT

LONDON

Introduction

The following account of the physiology and the experimental pathology of the thyroid gland has been difficult of compilation. The literature of the subject is enormous and it is far from easy in many cases to assess the value of the contributions and to estimate the bearing of one observation upon another. Some problems have been presented in some detail, and tentative conclusions suggested. Others, such as the relation of the thyroid to the other endocrin glands, and especially to the adrenal, have been scarcely touched because it would seem preferable to treat these questions rather from the standpoint of the other organs concerned than from that of the thyroid.

It is hoped that most of the important literature has been referred to, but I trust that I shall be pardoned for omission of any work of interest which has escaped my observation or the value of which has been underestimated.

The Physiology and the Experimental Pathology of the Thyroid Gland

The Earlier Theories as to the Function of the Thyroid Gland.—In Todd's Cyclopedia of Anatomy and Physiology, published in the years 1849-1852, may be found a learned and interesting article by Handfield-Jones dealing with the history of the subject and the state of knowledge

at the time the article was written. From this article many of the references to the old literature here referred to were obtained. Galen was probably referring to the thyroid body when he wrote concerning the glands in the region of the larynx: "These are always found more loose and spongy than others, and . . . have been created for the purpose of moistening and bathing all the parts of the larynx and the passage of the throat." Morgagni (*a*) also quotes the following, which makes it clear that Galen knew that the thyroid gland has no duct: "Now the neck has two glands in which moisture is generated. But from the two glands which are in the neck there come forth no vessels by which the moisture may flow out, as those do from the glands of the tongue."

The publication in 1656 of the Adenographia of Thomas Wharton, a Yorkshireman, marked an epoch in the history of anatomy. It deals with his own discovery of the duct of the submaxillary gland, and gives careful descriptions of the salivary glands, thymus, and so on. The results were originally given in his lectures at the College of Physicians in 1652. Wharton gives a good account of the anatomy of the thyroid gland, and notes that it is much more full of blood than any other gland. He gave the organ the name by which it has been known ever since (from θυρεός, a shield). He suggests four functions for the organ: (1) to take up superfluous moisture from the recurrent nerve; (2) to "cherish" the cartilages; (3) to lubricate the larynx and render the voice sweeter; (4) to contribute to the contour and beauty of the neck. The third function is the one favored by Galen and long remained in vogue.

Verheyen and Santorini were doubtful about the presence of a duct leading into the pharynx or trachea. Haller in 1776 dismissed the question of a duct, and grouped together the thyroid, the thymus, and the spleen as glands without ducts, which pour a special fluid into the veins, and so into the general circulation. This is not very different from the modern conception,—in regard to the thyroid at any rate.

As late as 1834 we find papers on the thyroid which show that the importance of the organ in the economy was scarcely suspected. But ten years later Simon put forward an interesting theory which has recently been revived by V. Cyon. Simon considered that the thyroid exercises a regulatory function on the blood supply to the brain, exerting also its secretory function in an alternating manner with the substance of the brain.

Handfield-Jones in the article above referred to, and which was written only a few years after Simon's paper, still finds it necessary to attack the theories which connect the thyroid body functionally with the organ of voice. He seems to give a half-hearted allegiance to Simon's theory.

Extirpation Experiments Upon Animals.—The earliest extirpation experiments upon animals appear to have been performed by Raynard. This observer reports that the treatment of goiter in dogs can be carried

out just as in man. Complete removal of the thyroid was successfully carried out in dogs of medium age and in old dogs, but in young animals death occurred within a few days. The post-mortem examination did not reveal the cause of death.

Astley Cooper gave some account of the structure of the thyroid and extirpated the gland from two pups ten weeks old. The animals recovered after suffering from stupidity and malaise. The animals were killed very soon after the operation. Cooper seems to have carried out some further experiments, the results of which were not published.

V. Rapp (quoted by Bopp) removed the thyroid from a dog and a goat without ill effects. But removal of a goiter from dogs proved rapidly fatal. Bardeleben (*a*) succeeded in extirpating the thyroid in dogs and rabbits without inducing any ill effects. Other experiments carried out at this period were of little import.

Moritz Schiff during the years 1856, 1857 and 1858 carried out a series of thyroidectomies upon various animals. Some rabbits, some rats, some fowls, and some dogs survived the operation, but several dogs, a cat, and a rat died after some days. He gives hardly any account of the symptoms observed. Schiff explains that owing to insufficient accommodation he was compelled to cease his observations after fifteen days.

In 1857 Hegar and Simon removed the thyroid from an old cat, which a month after the operation showed no symptoms. Eleónet in 1866 removed a goiter from a colt without ill effects.

The earlier results of Schiff were apparently read before the Royal Academy of Science in Copenhagen and then buried in a work on the formation of sugar in the liver. It is not surprising that they remained unnoticed for many years. Cretinism had long been recognized, and in 1874 Gull described the condition which Ord, in 1878, called "myxedema." In 1882 the Swiss surgeons noted the symptoms of "cachexia strumipriva," or "operative myxedema," after operations for goiter in the human subject.

After an interval of a quarter of a century Schiff was led by the observations of Kocher and Reverdin in Switzerland to take up the problem again. In 1884 he recalled his earlier experiments of 1856-1858, and published the results of a new series of investigations. In the rat and the rabbit, thyroidectomy was not followed by any serious result. In the dog and the cat, however, complete removal was fatal. He gives an admirable account of the nervous symptoms after removal of the thyroid in the dog, and states that these may be avoided by a previous graft of the thyroid of one dog into the abdominal cavity of another. Other symptoms noted by Schiff were general malaise, arrest of growth in a young cat, and in two cases edema.

It must be noted that some of these symptoms, particularly those of a nervous nature, are at the present time attributed to loss of parathyroid

tissue which must have occurred when the thyroid was extirpated in dogs and cats.

Wagner and others confirmed Schiff's observations, and it has been stated that the first named author found an increased response in the nerves to galvanic currents after removal of the thyroid (and parathyroids) in cats.

Horsley was the first to operate on monkeys. He states that a week after the operation fibrillary twitchings of the muscles were noted, and that these ceased on voluntary movement. The animal then became "cretinoid." There was a "myxedematous" condition of the subcutaneous tissues. The tremors were relieved by keeping the animal warm. According to Horsley there were swellings of the skin of the face and abdomen, due to the infiltration of the tissues by mucin. The salivary glands became enormously hypertrophied and the parotid gland produced large quantities of mucin.

We are not concerned in this place with the nervous symptoms described by Horsley, but it may be observed in passing that so far as I am aware no subsequent observer has been able to obtain these "myxedematous" symptoms in monkeys or in other animals. Horsley gives no detailed protocols of his experiments.

Removal of the thyroid from different animals was carried out by a number of observers during several succeeding years. The majority of these confirmed the general views of Schiff as to the effects of total extirpations of the thyroid. It must be remembered that at this period the possibility of a separate functional importance of the parathyroids was not suspected, so that while in dogs, cats and monkeys thyroids and parathyroids were always removed together, in the herbivora the two external parathyroids were left behind in what was called "total thyroidectomy." For, although the external parathyroids were discovered by Sandström in 1880 and by Baber in 1882, it was not until Gley (*a*) rediscovered them and demonstrated their functional importance in rabbits that experimenters gave them due consideration. This was in 1891.

Following Horsley's work we have to record communcations by Welch, Albertoni and Tizzoni, Fuhr (*a*) (*b*), Herzen, Rogowitsch and others. These all supported the view of Schiff as to the effects of total extirpations of the thyroid. But Philipeaux, Munk, Drobnick and some others were inclined to deny the supreme importance of the thyroid in the animal economy and attributed the untoward symptoms recorded by other workers to injury to nerves, reflex action, and similar causes. Munk's observations are specially interesting in view of the results obtained by some more recent observers (*vide infra*). He came to the conclusion that the chronic disturbance of nutrition in thyroidless animals is nothing more than "Gefangenschaftkachexie" which may often be observed in unoperated animals. He states that out of four monkeys operated on in England one

was sent to him as "myxedematous." The animal had nothing more than an ill-defined facial swelling, probably due to a carious tooth, and an intermittent paresis of a fore limb. The animal was, according to Munk, otherwise in good health and lived for ten months after the operation. Munk insisted that although removal of the thyroid is a dangerous operation, it does not follow that the thyroid is absolutely essential to life. And this statement must be admitted as justifiable, even if the survivals are due to thyroid or parathyroid tissue which is so placed that it cannot be removed. It will be necessary to return to this point.

The further account of Gley's work, as well as that of Vassale and Generali and Kohn, will be found in the section on the physiology of the parathyroids.

The experiments of Vincent and Jolly may be briefly recalled so far as they relate to the general question of extirpation of thyroids and parathyroids, and more particularly in regard to the effects alleged to be due to elimination of the function of the thyroid. On these points the general conclusions were: "Neither thyroid nor parathyroids can be considered as organs absolutely essential for life. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys show only transient nervous symptoms. Dogs, cats, foxes and prairie wolves frequently suffer severely and die. On the other hand, badgers do not appear to be affected by the operation.

"In no animals, not even in monkeys, have we been able to induce any swellings of the subcutaneous tissue, which is the most striking feature of myxedema in the human subject. We think, therefore, that the pathology of myxedema in the human subject must be more complex than simple thyroid insufficiency."[1]

Several previous observers from Schiff onwards had noted the fact that thyroidectomy in dogs and cats is by no means always fatal. At the same time there has been a tendency to disregard the exceptions, and when any explanations have been offered it has been suggested that they are due to parathyroids having been overlooked at the operation, or to the existence of accessory thyroids. Munk (*vide supra*) indeed is among the few observers who have laid due stress upon the cases of survival. This observer, as we have seen, admits that removal of the thyroid is dangerous, but not that the gland is an organ essential to life. We cannot assail the logic of the position that an organ which may frequently be removed with impunity is not "essential to life" and the results obtained by Vincent and Jolly forced them to extend the observation so as to include not only one thyroid but also the parathyroids.

According to Noël Paton a "contention that the removal of the para-

[1] On other points discussed in these papers the present writer has changed his opinion. This applies to the change of parathyroid into thyroid.

thyroids does not produce the train of symptoms terminating fatally, must in the light of the work of other investigators be explained as due to a failure to remove all the parathyroid tissue." Now, in the case of rabbits, Paton quotes Pepere to the effect that accessory parathyroids are nearly always found in the thymus in rabbits. So that in rabbits parathyroidectomy is only fatal in the few animals which happen not to have any parathyroid tissue in the thymus.

In the monkeys employed by Vincent and Jolly no symptoms of myxedema were observed when thyroids and parathyroids were completely removed. These results differ from those obtained by Horsley (*loc. cit.*), Murray (*c*) and Edmunds (*a*), who state that it is possible to induce myxedema by operation. Compare with the results obtained by Munk (*vide supra*) and Kishi. The last-named only recorded one death out of six. Our animals were subject to catarrh, and one died of some laryngeal affection, and it seems probable that as in the case of other animals, removal of the thyroid gland leaves monkeys in a condition in which they are less capable of resisting disease. Most of the animals were active, and but for loss of weight showed no ill effects. In confirmation of the results of Vincent and Jolly, observers have failed to find any trace of a myxedematous condition in such animals.

Fig. 1. Photograph of a group of thyroidectomized sheep taken five months after operation (after Simpson, Quart. J. Exper. Physiol.).

Carlson and Woelfel report that myxedema does not develop in thyroidectomized rabbits, at least in seven months, nor in the monkey in several months.

In some groups of animals age seems to make a great difference to the results both of thyroidectomy and of "complete" thyroparathyroidectomy. Sutherland Simpson found that removal of the thyroid with the contained internal parathyroids in thirteen adult sheep and sixteen lambs from seven to eight months old, led to practically no ill effects (see Fig. 1). As a result of a similar operation, three lambs about two months old became "typical cretins" (see Fig. 2).

The complete operation (thyro-parathyroidectomy) in four young lambs (five to seven weeks old) resulted early in acute and fatal tetany. Removal of the two external parathyroids from the three cretins when about one year old was followed by only slight symptoms. According to Simpson age is an important factor with regard to the effects of both thyroidectomy and parathyroidectomy. The "typical cretins" of Simpson are described as "small and stunted, with broad faces and rickety limbs. The wool was coarse, but did not tend to fall out." In some of the young animals (cats and dogs) operated on by Vincent and Jolly interference with growth was very striking but the other "cretinoid" symptoms were absent.

Fig. 2. Photograph of cretin lamb about one year old, and of normal lamb of eleven months (after Simpson, Quart. J. Exper. Physiol.).

Basinger in 1916 carried out an extensive research on thyroidectomy in rabbits. Out of 140 animals operated upon "typical cretinism" was produced in 86. The experiments were carefully controlled as to feeding, and selection of subjects and normals from the same litters. The thyroidectomy was performed at the age of 2 to 3 weeks when the body weight was about 175 gms. Great care was taken to remove all thyroid tissue, leaving the external parathyroids intact, but it was subsequently found that in a considerable proportion of cases minute bits of the gland had been left behind and prevented the onset of cretinism. In different litters the proportion of successful results varied from 25 to 90 per cent.

About two weeks after the operation the onset of cretinism was detectable. The hair became dryer than normal, did not lie smoothly and could easily be pulled out. Retardation of growth was noticeable as early as the third week; it was greatest from the eighth to the twelfth weeks. By the end of the tenth week the average weight of the cretins was 750 gms., while that of the controls was 1400 gms. The posture of the cretins was typical. The bones were short and the muscles of the limbs too weak to support the body weight. The bones showed a pseudo-rickety condition (Hofmeister's "chondrodystrophia thyreopriva"). The skin became increasingly dry and scaly and finally eczematous. The typical "pot belly" seen in human cretins developed. If undisturbed the animals remained immovable for hours. When stimulated they moved slowly and awkwardly. No evidence of the typical myxedema seen in human cases was

observed. Neither did the chronic, progressive cachexia described by Hofmeister appear in any of the cretins kept alive for a year.

Transfusion of normal blood serum into the cretins had no apparent effect on the condition. Some improvement, however, resulted from transfusion of serum from thyroid-fed rabbits. Feeding with desiccated thyroid gland substance markedly ameliorated the symptoms but failed to bring about entirely normal development. Discontinuance of the medication led to relapse. The cretins proved more susceptible than normal rabbits to the toxic action of thyroid feeding.

It seems clear from the experiments of Sutherland Simpson and others that in young animals removal of the thyroid (one or more parathyroids being left behind) will bring about a condition resembling cretinism in the human subject. In older animals symptoms may not be observed, but thickening and dryness of the integument with a tendency to loss of hair and wasting followed by adiposity have been described. It is stated that there is loss of muscular tone, and that regeneration of tissues is slower than normal. There may be anemia. The body temperature is low; the power of heat regulation is diminished (Lorraine Smith) and the animal becomes poikilothermic (Boldyreff); the sexual functions are interfered with. It has been stated that the limit of assimilation of carbohydrates is raised. "The nervous system is markedly affected, dullness and apathy being prominent symptoms. Many nerve-cells, especially those of the cerebral cortex, exhibit a shrunken appearance, and present a strong contrast with those of the normal animal" (Shafer). A myxedematous condition of the skin has been described by some authors, but the present writer has never seen this (*vide supra*).

According to Edmunds (*b*) complete extirpation of thyroid and parathyroids in dogs is frequently followed by cataract.

Thyroidectomy in the amphibia interferes with the normal metamorphosis, and retards or completely stops growth and ossification of bone. The operation does not appear to hinder the development of the gonads. (Hoskins, Terry, Allen (*a*).)

Several observers have reported a diminution in the alexins and opsonins in the serum after removal of the thyroid.

V. Eiselsberg described atheromatous changes in the aorta after thyroidectomy in lambs.

The Internal Secretion of the Thyroid and Its Nervous Mechanism

It used to be commonly stated that the internal secretion of the thyroid gland passes, not directly into the blood-stream, but indirectly by means of the lymphatics. But more recent investigations have rendered this theory very doubtful (Carlson and Woelfel).

Asher and Flack (*b*) utilized the observation of V. Cyon that the excitability of the depressor nerve is increased by the action of thyroid substance. They believe that the thyroid furnishes an internal secretion which increases the excitability of the depressor nerve, and augments the effect of epinephrin upon the blood-pressure. According to these authors the secretory nerves to the gland are the laryngeal nerves.

More recent investigation seems to point to the sympathetic as the origin of the secretory nerves to the thyroid. Rahe, Rogers, Fawcett and Beebe find that stimulation of vessels with the accompanying nerve filaments causes a diminution in the amount of iodin contained in the gland. These authors conclude that the thyroid is at least in part under nervous control, and that its physiologically active substance is discharged into the circulation in response to a nerve stimulus.

The view that the sympathetic fibers are true secretory nerves to the thyroid is supported by the observations of Cannon and Cattell upon the electrical response of the gland during activity. Control by the sympathetic suggests that adrenin may stimulate the thyroid to increased activity, and this was proved to be the case by intravenous injection of adrenin, and by stimulation of the adrenals through the autonomic nerves. By continuous stimulation (fusion with the phrenic) of the cervical sympathetic a condition resembling exophthalmic goiter was produced. It seems possible that the thyroid (like the suprarenal) has an emergency function, which would increase the rate of metabolism and augment the efficiency of the adrenin secreted simultaneously (Cannon and Fitz).

Rogoff tried to detect in the blood coming from the thyroids of three dogs a physiologically active secretion, tested by feeding tadpoles with the dried blood. Only one dog gave evidence of an active pouring out of thyroid secretion into the blood. In this case the blood was collected from the glands during massage and stimulation of the cervical sympathetic nerve. The number of experiments here recorded is not sufficient to warrant us in drawing any very definite conclusion.

The Nature of the Substance Secreted by the Thyroid and Its Physiological Actions.—A detailed consideration of the nature and actions of the various thyroid derivatives will be found in the chapter on "Chemistry of the Thyroid." Merely a few of the outstanding features will be mentioned here.

In 1895 Baumann (*a*) discovered the presence of iodin in the thyroid gland, and prepared a substance from it containing 9.3 per cent of iodin. The substance is known as "thyroidin."

Oswald (*b*) (*e*) in 1899 considered the iodin of the thyroid gland to be bound up in a globulin-like body, and the compound was called by him "thyreoglobulin."

Neither of these substances appears to have been chemically pure. More recently Kendall (*c*) (*i*) has isolated a white crystalline substance from

the gland. This substance he calls "thyroxin." The iodin content of thyroxin and the iodin content of the sulphate salt were found to be 65 and 60 per cent respectively. This established the molecular weight of 585. Ultimate analysis and a study of the derivatives of thyroxin show the structural formula to be 4, 5, 6 tri-hydro — 4, 5, 6 tri-iodo, — 2 oxy, — beta-indolepropionic acid. This substance is stated to possess the active properties of thyroid gland extracts and substances. It is stated that thyroxin possesses the remedial properties of thyroid gland substance as tested upon patients suffering from myxedema.

There is a delay in the action of thyroxin. Successive daily administration brings about death, but a single injection even of enormous doses, produces no effect. According to Plummer 1 mg. of thyroxin in an adult weighing 150 pounds increases the metabolic rate 2 per cent.

Kendall suggests that in the normal animal organism thyroxin is not fundamentally essential to life. This agrees with the results of extirpation experiments described above, and further is in accordance with the emergency theory of Cannon (*vide supra*). Kendall is of the opinion that thyroxin is a catalyst, and that its function is to increase the rate at which the fundamental chemical reactions of the body are carried out.

Intravenous injection of thyroid extracts or of thyroid preparations produces a marked temporary fall of blood pressure. There is, however, no reason to believe that the effect is specific. It is probably the same kind of fall as is produced by the injection of extracts of most organs and tissues in the body. The direct cause of the fall is a dilatation of peripheral vessels in different regions of the body. There is no evidence that this effect on blood-pressure has any bearing on the question of the internal secretion of the organ (see Vincent (*b*) (*c*), 1912, 1918). The substance which produces this fall, and which can be extracted from most of the organs and tissues in the body may possibly be histamine.[2] (Barger and Dale.)

In 1912 Gudernatsch made the interesting discovery that feeding tadpoles with thyroid substance causes precocious differentiation of the body, but suppresses further growth. The tadpoles begin to undergo metamorphosis a few days after the first application of the thyroid and weeks before the control animals do so. This observation has been confirmed by several observers, and the reaction is commonly supposed to be a delicate test for the presence of physiologically active thyroid substance.

But Swingle (*a*) (*b*) reports that tadpoles fed with potassium iodid, flour and algæ grew more rapidly and developed limb buds more rapidly than others fed with algæ only. According to this observer iodin is more effective than fresh thyroid tissue. Further, Allen (*b*) finds accelerated

[2] Histamin is closely related to histidin which is a common product of protein cleavage.

metamorphosis in tadpoles to result from the administration of iodin even after both thyroid and pituitary had been extirpated.[3]

Morse finds that iodized blood-albumin will produce these changes in metamorphosis. The reaction therefore is not a specific thyroid reaction. This writer suggests that perhaps the heightening of the opsonic index, which is known to result in other organisms after thyroid feeding, is responsible for the effects on the larvæ.[4]

The balance of evidence is in favor of the view that the effects first observed by Gudernatsch are not due to thyroid as thyroid but are the result of some non-specific action on the organisms of certain organic iodin compounds.[5]

It is stated that injection of an active thyroid extract into the circulation causes a markedly increased sensitiveness to adrenin as tested by the rise of blood-pressure caused by the administration of a certain dose of this drug. The observation is being used clinically as a test for hyperthyroidism. (Levy, Goetsch (*b*), Anon. Endocrin 1918.)

A further illustration of the action of the thyroid secretion on growth is found in the observation of Carrel that brain and other tissues grow *in vitro* increase several times as rapidly in the presence of thyroid substance as in its absence.

Several series of feeding experiments upon white rats have been carried out during the past seven or eight years.

Schafer in 1912 administered small amounts of thyroid to groups of white rats and found that the effect, especially in females, was to stimulate growth. There was a greater nitrogen excretion and greater nitrogen retention than in animals treated with substance from other glands.

Fordyce fed young white rats with thyroid and reports emaciation in all cases. The glands examined after death were full of colloid, while in the controls this was absent or small in amount. He considers that in animals treated with thyroid substance the colloid is retained, while in the others the glands are in active secretion and the colloid is rapidly absorbed.

E. R. Hoskins studied the effect of thyroid feeding on the growth of white rats, using animals from the same litter for comparison. He found that neither male nor female animals are affected in body weight by the treatment, and attributed the depressing effects upon growth and body weight obtained by previous investigators to a toxic effect produced by too large a dose.

Large doses caused hypertrophy of heart, liver, spleen, suprarenal

[3] For a further discussion of this subject see Uhlenhuth.

[4] See also Rogoff and Marine.

[5] Kendall states that the action on metamorphosis (which occurs with small doses of his "thyroxin") is not due to the organic nucleus, but is due to the iodin in the molecule, which breaks off as hypoiodous acid (HIO).

bodies and kidneys. The results confirm the generally accepted doctrine that hyperthyroidism produces a general acceleration of metabolism. Hoskins could not find any constant changes in the thyroid gland.

Herring (*b*) carried out a series of experiments in which each thyroid-fed animal and its control were taken from the same litter. He administered fresh ox-thyroid in daily amounts of from 0.1 to 0.2 gram. (This would correspond to 25 to 50 mg. of dried thyroid daily.) The control male rats (3) gained an average of 69 grams in 25 days. The thyroid-fed males gained 65 grams. In the female rats the controls gained on an average 2 grams more than the thyroid fed.[6] There was considerable variation among the female animals, which were more susceptible to the treatment than the males.

Cameron and Carmichael have recently tested the effect of thyroid feeding on white rats. They have taken the precaution to use animals from the same litter for comparison. Males and females were compared separately. Their dose was always based on the body weight of the animal at the time of treatment and was relatively small compared with that employed by previous observers. Some of the control animals were fed with liver substance instead of thyroid, and this was found not to affect the curve. They think that toxic effects may be ruled out.

The body-weight was found uniformly smaller in the thyroid-fed animals. The difference in weight between the control and the thyroid rats after prolonged feeding tends to diminish or disappear. This is at any rate true in females. The results appear to show that size of the dose has very little effect. This conclusion is opposed to that of previous observers. The thyroids of all the treated rats were paler than those of the controls.

The chief facts established by these experiments are that thyroid feeding inhibits the growth of young white rats, at any rate for the period of eight or nine weeks, and that iodid has no effect. These experiments afford the first definite chemically controlled test for thyroid as against iodid.

Kojima finds that thyroid administration as well as the giving of NaI and KI to the rat causes accumulation of colloid in the thyroid (v. Fordyce *supra*) and the epithelium of the vesicles become flattened. The cells of the parathyroid are generally swollen. This observer records diminution of body weight as a result of thyroid feeding. There is also hypertrophy of the pancreas accompanied by the occurrence of numerous mitotic figures in the nuclei and alterations in the granules of the cells.

We must now treat briefly a subject well known to students of endocrinology under the name of "experimental hyperthyroidism."

[6] In consideration of the variability of growth in rats of the same litter this difference cannot be regarded as significant. R. G. H.

In 1896 [7] R. H. Cunningham contributed a masterly article entitled "Experimental Thyroidism." In this will be found a full and very interesting account of the history of the subject up to that date. In Cunningham's work, and indeed in that of all subsequent investigators in this section of the subject, the question under discussion has been: "Can we induce symptoms of exophthalmic goiter by administering thyroid substance to animals?" Cunningham found, as the most trustworthy recent observers have found, that we cannot. Such symptoms as were noted, he attributed to an intoxication resulting from the ingestion of decomposed thyroid material. Moreover, similar effects could be obtained by treatment with other tissues. In his conclusions Cunningham states: "The effects resulting from the intravascular or subcutaneous injections of aqueous extracts, decoctions and the concentrated extractives of the thyroid tissue, of the thymus, of muscle, etc., are by no means necessarily indicative of the function and the action of the hypothetical internal secretions of the same tissues during life." This is a lesson which many modern writers on internal secretion have still to learn.[8]

Among those who claim that they have succeeded in inducing symptoms of hyperthyroidism in animals by thyroid feeding is Walter Edmunds. He employed "thyro-colloid" made from the thyroid glands of sheep by a process devised by R. Hutchison. In monkeys "well-marked symptoms were produced—namely, proptosis, dilatation of pupils, widening of palpebral fissures, erection of hairs on the head, the hair falling out in patches, paralysis of one or more limbs, emaciation and muscular weakness, and finally death from asthenia." There is no record that Edmunds carried out any control experiments. He gives sketches of a monkey before and after treatment.

In animals then, the results of experiments are differently interpreted by different observers and the actual symptoms found are variously stated. There seem to be few well authenticated cases in which the condition even strongly suggested that of exophthalmic goiter.

Carlson, Rooks and McKie have recently reached the conclusion that toxic symptoms can in all probability be produced in all animals by thyroid feeding. Some groups of animals are much more resistant than others. To what they owe their resistance is not clear. In the more resistant groups the symptoms are probably not specific thyroid effects, but complicated by the effects of the excessive protein diet. This applies

[7] Not published until 1898.

[8] There are, of course, many points in Cunningham's paper which would necessarily be stated very differently at the present day, but the chief doctrines and the general trend of the communication are in my opinion in accord with those of the most careful examples of recent work, various clinical writers to the contrary notwithstanding. Just as in the extirpation experiments there has been a tendency to find "myxedema" on very slight provocation, so in feeding investigations observers have rushed too soon to the conclusion that the symptoms they noted were those of exophthalmic goiter.

at any rate when large doses are given. The symptoms observed were loss of body weight, gastro-enteritis, and diarrhea. Thyroid feeding does not produce tachycardia, nervousness or exophthalmos. Although the symptoms in experimental animals may be those of "hyperthroidism" they are not those of exophthalmic goiter. According to Carlson and his co-workers, man is very susceptible to thyroid feeding and the expression of hyperthyroidism in the human subject may differ from that in the lower animals.

Thyroid substance is toxic, while substance prepared from brain, liver, spleen, kidney, and skeletal muscle is not toxic. The toxic substance is not due to autolysis or decomposition, and is not simply an excess of protein in the food. (French.)

In the case of animals very susceptible to thyroid feeding, dogs' normal thyroids are more toxic than the hypertrophied thyroids. As the latter contain less iodin, the toxicity of the dog's thyroid is directly proportional to its iodin content. (Stoland.)

Dogs, cats and rabbits show the same relative resistance to thyroid pressure liquid introduced intravenously and to thyroid given by the mouth. (Caldwell.)

According to Kendall (*d*) (1917) thyroid and adrenal cortex must act together in order to produce "hyperthyroidism."

How far the toxic effects referred to above are due to iodin quâ iodin has not yet been fully investigated, but Swingle (*a*) (*b*) has pointed out that since all the symptoms of "hyperthyroidism" can be produced in thyroidless frog larvæ by overfeeding with iodin, it is logical to suppose that the symptoms of hyperthyroidism in man are due to the same cause.[9] The whole difficulty at the present time lies in the fact that the symptoms of thyroid feeding in animals do not appear to be those of "hyperthyroidism" in man.

The Influence of the Thyroid upon Metabolism

In 1893 it was noticed that when patients suffering from myxedema were fed with thyroid gland substance there was a rapid loss in body weight, due to diminution of subcutaneous fat and water. From that time up to the present thyroid preparations have been used with good results to reduce obesity.

The study of this effect led to a series of experiments on the influence of the administration of thyroid glands upon metabolism. The majority of observers recorded a distinct increase of nitrogen in the urine, with a concomitant decrease in weight, indicating an increased protein metabolism.

[9] The symptoms of "iodism" in man are not, however, those of hyperthyroidism.

The discovery of iodin in the thyroid gland by Baumann and the claim that "thyroidin" was the "active principle" of the organ led observers to test the action of this last upon metabolism, and to compare its activity with that of the crude gland. Treupel, Grawitz and others, experimenting on the human subject, and Roos (*a*), who used a small dog, came to the conclusion that Baumann's "thyroiodin" influences metabolism in the same way as the thyroid gland substance itself, that is to say, the body weight diminishes and the nitrogen excretion increases.

Magnus-Levy (*a*) devoted special attention to the respiratory gas exchanges during thyroid administration. In normal individuals there was no very constant increase of the oxygen intake and the carbonic acid output. The effects were more marked in myxedematous patients. Thyroiodin showed qualitatively the same effects as thyroid gland substance. Potassium iodid did not produce the same effects.

Similar results have been obtained by other observers.

In all these experiments (which were of short duration) the increase of oxidation processes proves that the greater part of the loss of weight under thyroid feeding is caused by destruction of fat. The careful experiments of Schöndorff showed that after a certain period the protein is also attacked.

Considerable evidence has been accumulated that the metabolic activity of thyroid preparations depends on the amount of iodin present. Oswald (*e*), who worked with his "thyreoglobulin," found that a preparation poor in iodin produced little or no effect upon metabolism, while one rich in iodin produced a marked increase in the nitrogen excretion. Marine and Williams reached similar conclusions in regard to the efficacy of thyroids containing varying proportions of iodin.

According to Cramer, who gives full references, the administration of thyroid reduces the liver glycogen to a trace. He considers that the increased protein and fat katabolism is a secondary effect due to increased mobilization of the liver glycogen.

Frontali and Hunter (*b*) report the elimination of very large quantities of creatin in sheep and dogs after thyro-parathyroidectomy.

Brief reference has been made above to the effect of Kendall's thyroxin upon metabolism. Plummer (quoted by Kendall) has shown that 1 mg. of thyroxin in an adult weighing approximately 150 pounds increases the metabolic rate 2 per cent. The curve of this response has been shown to be approximately a straight line between metabolic rates 30 per cent below normal to 15 to 20 per cent above normal.

Quite recently Abelin has declared that certain amins derived from protein have the same action on metabolism as the administration of the thyroid gland itself.

Thyroid Transplantation

Very numerous thyroid transplantation experiments of different kinds and upon different animals have been carried out but it is not easy to gather from the literature how many of such experiments have been completely successful. It is quite clear that a large majority have been quite unsuccessful. The grafted tissue has rapidly degenerated and disappeared. In other cases a process of regeneration has set in and the grafted thyroid tissue has remained alive and presumably functional for many months.

Heteroplastic transplantations (the grafting of thyroid from one animal into another of a different species) is always unsuccessful. Homoio transplantation (grafting from one animal into another of the same species) can only have been successful in a small number of cases. Autotransplantation (grafting of pieces of thyroid of an animal into different regions of the same animal) was shown by Cristiani to be possible, that the grafts "take" and that they are functionally active for a long period. Another kind of transplantation has been recently studied by Loeb (*c*). This he calls "syngenesioplastic" (transplantation into nearly-related individuals of the same species). The results obtained by this method in guinea-pigs are intermediate between those obtained after auto- and homoio-transplantation. The thyroid behaves for a time like an autotransplanted tissue, but is finally destroyed by lymphocytic infiltration.

The vascular suture method of Carrel and Guthrie (*a*) (*b*) has placed at our disposal a means of grafting entire glands or lobes of thyroid. These authors removed the thyroid of a dog from its original position and replaced it in the neck. The vessels were anastomosed and circulation was set up. The gland retained its normal function.

Using this method, Stick and Makkas report ten cases—3 autoplastic, of which 2 succeeded, the subjects living 51 and 245 days, respectively. The rest of the cases (one autoplastic, 7 homoioplastic) were unsuccessful. The transplanted gland was found necrosed or not found at all.

Groves and Joll report what they consider to be a successful case of homoiotransplantation in the human subject. This was carried out by the old method (without vessel suture).

The Relation of the Thyroid to the Sexual Functions

A relation between the thyroid and the sexual functions in women has been popularly recognized for ages. The thyroid is relatively larger in women than in men, and this is specially noticeable during puberty, menstruation and pregnancy. The proper development of the reproductive

organs is dependent on the functional integrity of the thyroid. Sexual intercourse in both sexes increases the activity of the gland, and it is likely to swell in consequence. Married men under forty years of age are on the whole of better physique than the unmarried, a fact probably partly depending on the maintenance of thyroidal activity which marriage assures. The same applies to women. (McCarrison.)

There is considerable uncertainty in connection with the relations between the thyroid and the ovaries. It is stated that the ovaries exercise an inhibitory action on the thyroid; in fact, the latter becomes hyperactive after castration, and there is an increase of colloid matter. This is the cause, it is said, of the larger number of cases of exophthalmic goiter after the menopause. (Gley.)

It is possible that the relations of the thyroid to the organs of reproduction will be fully comprehended only when the part played by the adrenal cortex is understood.

The Relationship Between Thyroid and Parathyroid

The earlier investigators looked upon the parathyroids as embryonic thyroids and a belief in some kind of morphological and physiological relationship between the two glands has persisted, in one form or another, up to the present time. But for the past twenty years the majority of authors have inclined to the view that the parathyroid is to be regarded as an organ *sui generis*. The problem of thyroid and parathyroid resembles in some respects that of adrenal body and chromaphil tissue. In both cases we have to deal with two different kinds of tissues, of separate embryological origin, and presenting marked divergencies in histological and chemical characters. In both cases we see the two different tissues coming together in such a way as to present, from an anatomical aspect a single organ. It is not clear, from an *a priori* standpoint, whether we ought to expect that the anatomical conjunction implies any kind of physiological coöperation. In the case of the adrenal and the chromaphil tissue there is very little evidence in favor of any physiological relation. In regard to the thyroid and parathyroids the experimental evidence has been somewhat contradictory. Jolly and the present writer, as well as some other authors, have reported that on microscopical examination of parathyroids left *in situ* after removal of the thyroid, an alteration in structure had occurred. The parathyroids were said to have developed vesicles resembling those of the thyroid. The experiments were carried out upon dogs and cats.

A recent series of experiments upon rabbits by Arnason and the present writer does not lend support to the view that parathyroids left behind after thyroidectomy become converted into thyroid tissue. It is

possible that in the experiments on dogs and cats, in which species the parathyroids are in close proximity to the thyroid, a shred of thyroid tissue was left behind in the operation for thyroidectomy.

But it is certain that in certain pathological conditions the parathyroid may contain vesicles resembling those of the thyroid, and the present writer has collected other evidence of functional relationship between thyroid and parathyroid. (See Vincent (*b*), 1912.)

Summary

The Function of the Thyroid Gland.—There can be no doubt that the thyroid furnishes a substance or substances which are of the greatest importance to the normal growth and metabolism of the body. One or more of these substances appears to be an iodized derivative of protein—probably an iodized amin. The most striking of the activities displayed by the active principle or principles is to stimulate katabolism, though there are indications of an anabolic principle. Perhaps two separate active substances may be concerned in these two antagonistic influences.

There is some evidence that the secretion of the active substance is under the control of the sympathetic nervous system.

Is the activity of the substance secreted by the thyroid brought about by immediate influence on the organs and tissues themselves, or is the influence mediated, and effected through the agency of the nervous system? Each of these views may be supported by arguments of no mean weight.

The importance of the thyroid varies in different classes of animals. Sheep quietly grazing in a field may, and do, get on very well without a thyroid, while the hungry and active carnivore who preys upon them will suffer severely from loss of the gland.

Though we are beginning to understand something of the chemical aspects of metabolism as influenced by the thyroid, the morphological processes which are also influenced present problems which have received so far relatively little attention.

The current view of internal secretions in general and of the secretion of the thyroid in particular, has changed somewhat since the word "hormone" was invented. The modern conception is not so much that of a series of excitants sent out to stimulate the activity of different organs and tissues, as that of the existence of a certain essential minimal amount of each active substance and the maintenance of some proportion between the amounts of each (Paton).

According to Kendall, the physiological action of the thyroid substance is probably that of a catalytic agent. The fundamental reactions

are not altered qualitatively, but their rate is increased when thyroid derivatives are administered.

The so-called antitoxic action of the thyroid is probably directly related to its metabolic function. The diminution of the alexins and opsonins (*vide supra*) in thyroidectomized animals may be a natural result of retarded exchange of material in the tissues and will render the animals more liable to infection.

It would seem that iodin, in certain organic combinations, is valuable as a catalytic agent in aiding or hastening the fundamental metabolic activities of the body. The thyroid is an organ whose function is to utilize this fact for the needs of the economy.[10]

[10] Kendall believes that the essential part of the active substance is the NH_2COOH group, and that the iodin modifies the action, but is not essential. But he has not yet succeeded in preparing the active nucleus without iodin. "Thyroxin" has now, I believe, been synthesized on a commercial scale.

The Biochemistry of the Thyroid Gland . . *A. T. Cameron*

Introduction—Elementary Composition of the Normal Thyroid Gland—Compounds Present in the Normal Thyroid Gland—Bearing of the General Biochemistry of the Halogens on Their Presence in the Thyroid Gland—Iodin Content of the Normal Thyroid Gland—Forms of Iodin Combination—Evidence of Connecting the Iodin Compounds with the Internal Secretion—General Discussion—Discussion of Individual Substances—Relationship between Iodin Content and Thyroid Activity—Chemistry of the Pathological Thyroid Gland—General Conclusion.

The Biochemistry of the Thyroid Gland

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Introduction

From a biochemical standpoint the chief problems concerned with the thyroid gland are the chemical nature of the compounds present in the internal secretion elaborated by the gland, the mechanism of their manufacture, and their chemical effect. Of the first and third of these problems we are commencing to know a little; it is only possible to correlate a few facts which may perhaps be concerned with the second problem.

The outstanding feature which differentiates the thyroid gland from all other tissues in vertebrates is the constant presence of measurable amounts of the element iodin in normal individuals. Consequently any discussion of the nature and function of the secretion must consider the importance of iodin as an indispensable constituent, and contrast the relative effects of other iodin-containing substances; this leads naturally to a consideration of the relative positions of iodin, biochemically, compared with the other halogens, especially as all four are stated to be present in the gland.

Recently, considerable advance has been made in our knowledge of the form of combination of iodin in thyroid tissue; a crystallizable iodin compound has been isolated from the cleavage products. It will be necessary to refer to this important advance in some detail.

Finally, a brief account will be given of our present knowledge of the chemical variations accompanying pathological conditions of the gland.

The Elementary Composition of the Normal Thyroid Gland.—The following elements have been reported present: C, H, O, N, S, P, Na, K, Ca, Mg, Si, As, F, Cl, Br, I. There does not appear to be any record of analyses of the first three of these in whole thyroid tissue. Zunz (*a*) (*b*) (1919) found for dry fat-free tissue of normal men killed in war a nitrogen content varying from 12.46 to 14.82 per cent, the mean value being 13.8 per cent (corresponding to about 4 per cent for fresh tissue).

Morgenstern (1912) examined 50 human thyroids for Ca, Mg, S, P, and I. Twenty-two were pathological; ten of these contained Mg. It

was present in one other gland apparently, but not definitely nonstrumous, and Morgenstern concluded that it is probably only present in pathological (strumous) tissue. The extremes found were 0.006 and 0.009 per cent (mean 0.008). Excluding the 22 pathological thyroids, analysis of Morgenstern's figures shows the following average percentages (the extreme figures are given in brackets): Ca, 0.4 (0.09—1.3); S, 0.2 (0.04—0.65); P, 0.19 (0.08—1.2); Cl, 0.25 (0.13—0.45); I, 0.013 (not found in 8 cases; maximum observed 0.054). All these results were for fresh tissue.

The phosphorus content of the thyroid has been exhaustively examined by Fenger (*b*) (1913-15). For beef thyroids the variations are 0.6 to 0.8 per cent (fetuses), 0.4 to 0.9 per cent (adults), for dry tissue. The average content for nearly 4,000 beef thyroids was 0.4 per cent, dry tissue, or 0.12 per cent, fresh glands. The dried glands from male human fetuses contain 0.72 per cent; from female, 0.79.

Normal human thyroids have an average silicon content of 0.0082 per cent (Schulz). Gautier found arsenic in thyroid (0.00005 to 0.0009 per cent, fresh tissue). Its presence is denied by Hödlmoser.

Labat (1913) found bromin present in 16 of 24 human thyroids examined, in amounts varying from 0.00007 to 0.003 per cent for fresh tissue. Baldi (1898) had found 0.035 per cent, but his method probably lacked accuracy.

Gautier and Clausmann (1913) found in fresh human thyroid 0.00054 per cent of fluorin, and in sheep's thyroid 0.00046 per cent (dry tissue: 0.00212 and 0.00162 per cent).

Macadam (1854) having demonstrated that iodin was present in a number of edible plants, concluded that it should be present in the higher mammals, including man, but was unable to detect it. Kocher (*c*) (1895) suggested that since both thyroid extract and iodin have a beneficial effect on cachexia thyropriva, iodin might be a constituent of the gland. At his suggestion Tschirsch tested the gland for iodin, iodides, and iodates, with negative results. Almost immediately afterwards, Baumann (*a*) (*b*) (1895) announced his discovery of iodin in thyroid tissue. He found it invariably present in sheep and human glands, and to a less extent in goitrous glands and in hog thyroids. Subsequently (1896) from data for a large number of human glands he obtained the extremes: a trace to 0.46 per cent iodin in dried tissue, the average content being 0.09 per cent. He found iodin absent from the thyroids of many children, and usually present to a smaller degree. The thyroids of dogs, horses, cattle, swine, and rabbits all contained iodin.

Many researches have since been devoted to the confirmation and extension of these results of Baumann. Much of the work has been vitiated to some extent by the absence until recently of reliable chemical methods for the detection of small quantities of iodin in the presence of organic matter.

The whole subject will be treated at greater length subsequently; it may be stated here that iodin is an invariable constituent of normal thyroid tissue in all vertebrates, the observed extremes being 0.01 and 1.16 per cent for dried tissue; other mammalian tissue never contains amounts above the order of 0.001 per cent.

Ash.—The ash in beef thyroids is just over 4 per cent for dry tissue; 1.2 per cent for the fresh gland (Fenger, 1914).

Compounds Present in the Normal Thyroid Gland.—*Water.*—The ratio of weight of fresh to dry tissue varies between the limits 3 : 1 and 6 : 1 (66 to 85 per cent water). The variations appear to depend to some extent on species and to a greater extent on age. Sex does not appear to exercise an appreciable influence, but castration lowers the water content. The table on page 249 illustrates most of these conclusions. The effect of age is shown by the following percentage figures for cattle: 3-months fetuses, 84.1; 7-8-months fetuses, 82.3; 6 to 8-weeks calves, 74.3; adults, 72.6 (Fenger, 1912). Seidell and Fenger's (*b*) (1913) figures show a seasonal variation in water content, the percentage being less in summer.

Intermediate or End Products of Metabolism.—Marshall and Davis found 0.03 and 0.037 per cent of urea in the fresh thyroid tissue of two dogs, this being approximately the amount present in all the tissues of the body with the exception of the urinary apparatus. Von Gorup-Besanez (1856) noted the presence of lactic acid, which was confirmed by Bubnow, Moscatelli, and Hutchison.

Cholin is present in the thyroid (Blanchetière and Chevalier, 1909; Lohmann, 1911) as in most of the other tissues of the body. Lohmann also extracted a crystalline substance which he suggested was δ-aminovalerianic acid.

Von Gorup-Besanez found leucin, volatile fatty acids, and hypoxanthin. W. Kühne (1868) found in addition xanthin and succinic acid. Bubnow and Hutchison confirmed the presence of xanthin and hypoxanthin, and found in addition creatinin.

These compounds are all normally present in the different body tissues.

Carbohydrates.—Blumenthal (1893) obtained an osazone with m.p. 153°C., which he concluded was a pentosazone. Grund (1902) stated that dried beef thyroids contain 0.5 per cent of bound pentose. Glycogen is present (Marie Ramberg and de Kieselbach); the thyroid contains an average of 0.27 per cent, an amount similar to that in the adrenal (Marañón).

Fats and Lipoids.—Iscovesco (1913) isolated a number of different lipoids from sheep's thyroid, amounting to a maximum of 15 per cent of the dried gland. One of these, soluble in petroleum ether, and insoluble in acetone, is stated to have marked effects on general growth, stimulating

that of growing animals (rabbits), decreasing the weight of adults, and producing definite hypertrophy of specific organs.

The petroleum ether-soluble portion of beef thyroids (from several hundred animals) consisting chiefly of fat, averages 4.2 per cent of the fresh gland (containing 75.5 per cent of water) and of this 0.13 per cent consists of phosphatides, calculated as lecithin (Fenger (*e*), 1916). Thyroid tissue contains no more phosphatides than ordinary muscle fiber, in marked contrast to the other ductless glands which all contain much larger amounts. Fenger considers that this indicates that lipoids play no important part in the internal chemistry of the thyroid; evidently Iscovesco's results require confirmation.

Fenger's (*a*) earlier papers indicate considerable variation in the fat content of individual glands. There is a steady increase in the growing animal, in cattle thyroids from 1.1 per cent for 3-months fetuses to 8 per cent for adult cattle (1912). Bulls show a smaller amount (7 per cent) than steers (10.7 per cent), and pregnancy produces no definite effect (9 and 9.3 per cent, respectively, for pregnant and non-pregnant cows) (1914).

Proteins.—A summary of earlier work is given by Bubnow (1883) and by Oswald (*b*) (1899). Only two definite proteins have been isolated from the gland, *iodothyroglobulin,* and a nucleoglobulin (Oswald). This part of the subject will be reviewed in connection with the iodin compound of the gland.

Enzymes.—Thyroid tissue contains a lipase, a catalase, and is relatively rich in nuclease. The lipolytic capacity of the thyroid gland is equal to that of the spleen and testes, and only inferior to that of the liver and pancreas. The lipase acts strongly on esters of the lower fatty acids, less strongly on natural fats, and that from thyroids of carnivora is more active than the corresponding preparation from herbivora. It is readily extracted by water, but only to a smaller extent by glycerol (Yushchenko (*a*) (*b*) (*c*), 1910, 1911). An oxidase is present (Goldenberg).

The Bearing of the General Biochemistry of the Halogens on Their Presence in the Thyroid Gland.—Excluding certain of the earlier analytical methods, by which, through impurity in chemicals or inaccuracy of technique, iodin was found universally distributed, until recently the methods employed led to minimal values, and small amounts of iodin frequently escaped detection. From this cause especially arose the finding that iodin, though generally, was not invariably present in normal thyroid tissue. At present, three accurate methods are available, those of Bourcet (*a*) (1899), Hunter (*a*) (1910), and Kendall (*a*) (1914). The first permits the measurement of 0.00003 per cent of iodin with accuracy, but is tedious and requires large amounts of material. Hunter's and Kendall's methods, with 0.5 gram of material, detect the presence of 0.001 per cent of iodin; the latter gives greater certainty of a negative result in absence of

iodin. Numerous observations are available, based on one or other of these methods; utilizing some of these, and critically examining others, it has been possible to draw fairly definite conclusions as to the general distribution of iodin in living tissue (Cameron (*b*) (*c*) (*d*), 1914-1915).

Iodin is an invariable constituent of marine Algæ (limits, dried tissue, 0.001 to 0.7 per cent). Individual plants of the same species show considerable differences; in the more complex Algæ (as *Nereocystis*) it is possible to show differences in different parts of the same plant. Land plants contain much less iodin, though it is widely distributed. They exhibit the same variations, showing a differentiation not only determined by the species, but apparently by the plant cell also. All marine animals contain iodin. As advances in evolution occur there is more differentiation and probably less total iodin in the whole organism. The horny skeleton of sponges and corals is rich in iodin. Much of the material which has been found to contain marked quantities of iodin is in the nature of a secretion on to the outer surface of the body (e.g. annelid worm tubes, ascidian tests). In vertebrates the thyroid alone is of importance as an iodin containing tissue. Normal thyroid (dried tissue) contains at least 0.01 per cent. Nearly all other mammalian tissue contains much less than 0.001 per cent. Kendall recently found that a commercial desiccated preparation of beef pituitary contained 0.0025 per cent (quoted by Hoskins, 1920); Bourcet (1900) found for rabbit hair 0.0018 per cent, and fresh skin 0.0006 per cent, concluding that this indicated the chief channel of iodin elimination. In kidney tissue of the dogfish 0.003 per cent has been observed.

In the lower organisms there is evidence of a wide comparable distribution of chlorin, bromin, and iodin (e.g., see Mörner (*a*), 1907), but the observations are insufficient to permit conclusions to be drawn as to the relative functions of these halogens. All four halogens are present in thyroid tissue; but only chlorin and iodin in appreciable amounts. Until recently reliable methods for the estimation of small quantities of bromin and fluorin were wanting.

Chlorin is present in all vertebrate tissue in an ionised condition. There is no definite evidence that it exists in mammals in organic combination. Its importance is usually considered to consist in its availability, as the least toxic anion, to assist in the establishment of a definite osmotic pressure in intra- and extra-cellular tissue fluids, its non-toxicity being an inherited immunity from our marine ancestors. Its presence in the thyroid is therefore not significant.

Labat found bromin present in the majority of human thyroids, the maximum observed being 0.003 per cent, fresh tissue (0.01; dry tissue). Most of the other tissues examined showed no distinct trace, although human urine invariably contained 2 to 3 mg. per liter. The results indicated a slight selective action of thyroid tissue in retaining bromin. The

average amount present is of a lower order than that of iodin, and its presence in the gland is probably without significance. Numerous experiments have been carried out on the effect of bromid medication (cf. Wolff and Opp, who give a complete account of the literature) and the general consensus of opinion is that the bromid ion acts passively in replacing the chlorid ion.

Our knowledge of fluorin distribution is based on the work of Gautier and Clausmann. Their method is probably the only accurate one, but it is difficult and tedious and has not been tested by other workers. They conclude from their results that fluorin is localized in a specific fashion, accompanies phosphorus, and is concerned with phosphorus metabolism. The amount in thyroid (0.002 per cent, dried tissue) is of the same order as that in most of the body tissues.

Iodin, therefore, is the only halogen present in marked amount in thyroid tissue, and in thyroid tissue only, in vertebrates.

The Iodin Content of the Normal Thyroid Gland.—Iodin has been found in the thyroids of five species of elasmobranch, and one of the holocephaloid fishes, of one amphibian, two reptilians, six species of birds, and fourteen species of mammals. Wherever accurate methods have been employed the minimal figure found for dried tissue was at least 0.01 per cent. The following maxima have been observed (figures in percentages, dry tissue): fish (*Scyllium*), 1.15 (Cameron (*a*), 1913); birds (scoter), 1.14 (Cameron, 1915); sheep, 1.05 (Hunter and Simpson); dogs, 0.69 (Marine and Lenhart, 1909); man, 0.59 (Seidell); stags, 0.54 (Blum, 1899); pigs, 0.53 (Seidell and Fenger, 1913); cattle, 0.48 (Marine and Lenhart (*b*) (*c*)).

Most of the investigations for human thyroids have been obtained for tissue from individuals dead through various causes, which conceivably may have affected the gland though it appeared normal. Recently Zunz (1919) has determined the content in glands from normal men killed in war. His extremes are 0.044 to 0.426 per cent, dried tissue (0.011 to 0.121 fresh tissue). The whole thyroid contained from 0.00315 to 0.0449 gram of iodin, the mean being 0.01553 gram. His figures indicate that the thyroids of normal individuals have a much higher iodin content than those of individuals dead from disease.

The following table illustrates some further points in connection with the distribution of iodin in the thyroids of different species. The figures have been selected as far as possible from data for large numbers of normal individuals, whose thyroids were collected under similar conditions.

These figures for iodin content are derived from the following sources: for fish, birds, guinea pigs and dogs, Cameron, (1914, 1915); for American hogs, sheep (the percentage of iodin is much lower than the yearly average), and cattle, Fenger (1912, 1914); for English sheep, Martin (*a*) (*b*); for man, Baumann (*b*) (1896); for normal man, Zunz.

Animal	Sex	No.	Average Weight kg.	Average Weight of Thyroid		Average Per cent of Water in Thyroid %	Average Iodin Content of Thyroid mg.	Iodin in Dried Thyroid (Not Fat Free) %	Mg. Dry Thyroid Tissue per kg. Animal	Mg. of Thyroid Iodin per kg. Animal
				Fresh g.	Dry g.					
Dogfish (*Squalus*)	Male	75	2.3	0.091	0.0144	84	0.030	0.210	6	0.013
	Female	37	5.1	0.183	0.0297	84	0.056	0.189	6	0.011
Ratfish (*Hydrolagus*) .	Male	17	0.45	0.012	0.0030	76	0.018	0.620	7	0.040
	Female	17	0.93	0.062	0.0120	80	0.073	0.609	13	0.078
Pigeons	Mixed	24	0.27	0.040	0.0058	76	0.027	0.477	21	0.099
Crows	"	9	0.32		0.0088		0.065	0.751	27	0.202
Marble Murrelets	"	7	0.36		0.006		0.020	0.31	17	0.055
Guinea-pigs	"	15	0.44	0.058	0.0113	80	0.013	0.113	26	0.028
Dogs	"	11	16.9	3.73	1.011	73	0.982	0.098	60	0.088
Hogs	"	200		8.8	2.90	67	7.83	0.24		
Sheep (American)	"	200		8.9	1.96	78	1.18	0.06		
" (English, 1912).	"	3280		2.83	0.83	71	2.59	0.343		
" " 1913).	"	6964		2.60	0.62	76	2.46	0.407		
Cattle	Bulls	470	636	30.0	9.0	70	19.4	0.215	15	0.042
	Steers	1068	545	23.0	8.1	65	19.7	0.244	17	0.060
	Pregnant cows	1123	454	24.4	7.5	69	18.5	0.247	17	0.060
	Non-pregnant cows and heifers	1021	420	22.6	7.0	69	17.0	0.243	17	0.059
Man	Male	15	(70)		6.22		5.40	0.086	89	0.077
	Female	26	(60)		4.85		4.31	0.089	81	0.072
"	Male (normal)			(8.5-59.2)		75	15.53	(0.2)		

The table shows that while the relative amount of thyroid tissue appears to increase with evolutionary development, this is not paralleled by the corresponding iodin content. The figures for sex are not sufficiently numerous to permit a definite conclusion, though those for cattle thyroids, based on a very large number of individuals, would seem to indicate definitely that both thyroid and total iodin are relatively greater in the female; on the whole, my figures for fish thyroids support this conclusion of Fenger's. Castrated animals resemble females.

Age seems a definite factor. For human thyroids Monéry (1904) found the maximum iodin content between 40 and 60 years, an increase between 15 and 40, and a decrease after 60. Aeschbacher (1907) found for the first 25 years an average of 2.34 mg., from 25 to 30 years, 8.98, and over 50, 4.6 mg. Pellegrini (*a*) (*b*) (1915) obtained his highest figures, 7 mg., between 45 and 55 years; from 55 to 65 years, 3 mg.; lowest figures below 15 years. These figures are based largely on pathological material but are in accord and can be considered relatively correct.

Fenger's more reliable figures for normal animal tissue show a similar variation. Cattle fetuses, 6 to 12 weeks old, showed respectively for 20 males and 20 females, 0.07 and 0.08 per cent iodin in the desiccated fat-free gland. For 4 to 5 months fetuses (6 males, 9 females) the figures were 0.31 and 0.20; for 6 weeks' old calves (17 males, 23 females) 0.21 and 0.25. For adult cattle the figures were 0.28 and 0.35. Similar results were obtained for ewes and sows and their fetuses, the figures indicating a definite relation between the amount of iodin in the gland of the pregnant animal and in those of the corresponding fetuses; the latter are distinctly smaller (Fenger, 1912). Correspondingly small figures were obtained for human fetuses (1915).

Seidell and Fenger find a distinct seasonal variation in the iodin content of American sheep, hog and beef thyroids (cf. also Fenger (*f*), 1918). The percentage between June and November is in general from two to three times that between December and May. Onset of severe cold weather is followed in a week or two by noticeable enlargement of the cattle glands, and lowering of their iodin content. Sheep show this change, but to a less extent (the figures for sheep in the table illustrate the inverse ratio which appears to exist between size of gland and iodin percentage, even in normal animals of the same species). Water, fat, ash and phosphorus content parallel the change in weight of the gland. The conclusion is drawn that phosphorus does not form part of the active iodin complex, but only of the glandular tissue, and that neither the composition of the active iodin complex nor that of the supporting tissue of the gland changes with season, but only the relative amounts of the two. It is pointed out that Martin's figures for English sheep and Guyer's for Scotch sheep show a much smaller variation but in the same direction. Seidell and Fenger consider that diet is insufficient to explain the seasonal varia-

tions. These observers declare they can best be accounted for by metabolic changes due to temperature, and further state that "during the colder months of the year the increased physical activity of animals, together with the necessity for maintenance of the normal body temperature in a colder surrounding medium requires an increased metabolism which in turn would no doubt call for an increased output of the active thyroid material. Conversely, in the summer months, the demands upon the thyroid being less than the normal rate of production of active principle, would lead to a storing up of the iodin compound."

Undoubtedly the factor most definitely and quickly able to cause variations in iodin content of the thyroid gland is diet. Baumann (1896) suspected high iodin percentages to be due to iodin administration and stated that an increase is caused by feeding with sea-fish, beef-thymus, and especially with thyroid itself or iodothyrin, and with plants the ashes of which contain iodin (sugar-beet), while feeding raw meat to dogs lowers the iodin content. Baumann and Goldman fed a dog raw meat. One thyroid lobe removed weighed 1.92 grams and contained 0.06 mg. iodin. The animal was then fed for a month on dried stock-fish. The remaining thyroid lobe was then removed, weighed 2.5 grams, and contained 2.9 mg. iodin. Roos (1899) and numerous other workers have obtained similar results. Roos pointed out that the glands of carnivora usually contain smaller amounts of iodin than those of herbivora, corresponding to the fact that raw meat contains no detectable iodin. The most striking examples of the results of feeding iodin are those of Simpson and Hunter. Continued daily administration for six weeks of small quantities of sodium iodid raised the iodin content of a sheep's thyroid from 0.53 to 1.15 per cent (dried tissue). Hunter and Simpson also furnish the best example of such increase on a natural iodin diet. The dried glands of 10 Orkney sheep, which had been allowed to run wild and feed largely on sea-weed, contained amounts of iodin varying from 0.42 to 1.05 per cent of iodin. The average of this particular group was 0.71, a much higher figure than any previously recorded. The only comparable figures to these maxima are Cameron's for the dogfish *Scyllium*, 1.16, and the sea-scoter, 1.14. The marine diet of these animals is definitely rich in iodin. The figure for crows (0.75 per cent) was obtained for birds feeding largely on clams, the dried flesh of which contains about 0.01 per cent of iodin. (The harmony between the highest maximal figures suggests that these represent a state of complete saturation of the gland with iodin.)

Bourcet (1901), discussing the probable sources of thyroid-iodin, pointed out that traces of the element are contained in various fruits and vegetables, such as fish, mollusks, milk and eggs, and also French wines. Further information as to probable sources of the element is given in the papers of Bohn and of Forbes and Beegle.

The work of Marine and coworkers indicates that iodin, fed or in-

jected as iodid, reaches and is retained to a considerable degree by the thyroid in very short time (when injected into a vein, within a few minutes; cf. also Blum and Grützner; Boruttau considers that true storage of iodin does not occur).

In view of these facts it seems possible that part of the seasonal variation found to exist by Seidell and Fenger can be referred to changes which normally occur in the iodin content of a changing diet.

The distribution of iodin within the gland is not known with certainty. Justus (1902) using a histochemical method, claimed to have shown that each cell nucleus contained iodin, and that the iodin content of the colloid was much smaller. Babij (1913) showed his method to be incorrect. It is well established that feeding with iodids or thyroid increases the colloid material of the gland (Fordyce, Kojima, Cameron and Carmichael) whence it would appear probable that the iodin is chiefly contained in the colloid, especially as this is commonly regarded as the form of storage of the internal secretion. Oswald (*d*) (1902) found that only those glands which on microscopic examination appeared free from colloid contained no iodin (detectable by Baumann's method). Claude and Blanchetière, using an inexact chemical method, found considerable iodin in diseased glands containing scarcely any colloid. Pellegrini (*b*) (1916) states that there is no definite relation between the amount of colloid and of iodin per gram dry substance of the human thyroid. Tatum (1920), utilizing the fact that frozen section preparations of unfixed thyroid glands do not retain the colloid when floated in isotonic salt solution, separated the colloid from the cell material, and found iodin in both cells and colloid of beef, sheep, and pig thyroid glands. The ratio of iodin percentage in cells to that in whole glands appears to be relatively constant, even though the glands vary both in morphology and in total iodin content. Bensley's results are discussed in another section of this article.

The Forms of Iodin Combination in the Thyroid Gland.—It will be instructive, before dealing with the thyroid gland itself, to consider what is known of iodin compounds present in other tissues. Okuda and Eto (1916) found that nearly all the iodin present in algæ is in soluble organic non-protein combination, a trace only being present as iodid. Drechsel (*a*) (1896) found an iodo-amino-acid in the digest from the horny skeleton (gorgonin) of the coral *Gorgonia cavolinii,* which was subsequently identified as 3.5 diiodo-l-tyrosin (Wheeler and Johns); Mörner (*b*) (1913) found that bromin is similarly combined in corals as dibromtyrosin. Wheeler and Mendel showed that diiodotyrosin is present in sponges. Oswald (*h*) (1911) found that the amount of diiodotyrosin obtainable represented only 7.4 per cent of the total iodin present in gorgonin, and only 15.7 per cent of that in spongin. He concluded that more than one iodin compound was present. Similarly, Mörner obtained dibromtyrosin corresponding only to 2.5 per cent of the total bromin present, and drew a simi-

lar conclusion. Wheeler and Clapp adduced some evidence that p-iodophenylalanin may be present in sponges.

All attempts to isolate these or similar amino-acids from the thyroid have failed.

Most, if not all, of the iodin in the gland is in organic combination. Blum and Grützner consider that there is a small amount of iodid present.

Baumann (1895), having detected iodin in the thyroid, endeavored to isolate the iodin compound. He boiled fat-free tissue with about four times its weight of 10 per cent sulphuric acid until only a slight brown residue was left; this was extracted several times with boiling 85 per cent alcohol; the extract evaporated to dryness constituted Baumann's "thyroidin" (*iodothyrin*). A pepsin digest of the fresh gland gave the same residue. It contained about 10 per cent of iodin which was scarcely at all split off by alkalis. Iodothyrin was considered to be united to protein in the gland. It was amorphous, gave no biuret reaction, was almost insoluble in acids and water, easily soluble in alkalis and precipitated by acids without decomposition. It amounted to about four per cent of the total weight of the dried gland (Baumann and Roos). Roos (1896, 1898) obtained the preparation by digestion with acids, removing fat with ether, and twice precipitating with acids from alkaline solution. The final product contained 9.3 per cent of iodin. His elementary analyses for preparations from sheep and human thyroids show only moderate agreement and great variation in iodin content (respectively, I, 1.31, 4.31 per cent; S, 1.40; N, 8.91, 10.41; C, 57.04, 61.41; H, 7.28, 7.43; Ash, 0.4, 0.47; Cl, 0.4, 0.5). Iodising iodothyrin gave in two preparations 10.89 and 10.3 per cent iodin. According to Blum (1898) iodothyrin is an inconstant decomposition product of thyroid tissue, different successive extracts containing different percentages of iodin; the maximum he obtained was 8.9. Nürnberg (1907) considered that the iodin compound present was iodotryptophan.

Other preparations obtained from thyroid are S. Fränkl's "thyreoantitoxin," considered to be $C_6H_{11}N_3O_5$, Notkin's "thyroprotein" (1896), and those of Drechsel (*a*) (1895). With the exception of Baumann's, none of these can any longer be considered to have any physiological significance. Critical consideration of these preparations and of earlier similar work, is given by Oswald (*b*) (1899), who succeeded in removing all the iodin from thyroid tissue by repeated extraction with physiological saline solution. The extract contained two proteins, one salted out by half saturation with ammonium sulphate, the other by complete saturation. The first, *iodothyroglobulin,* contained iodin and no phosphorus, the second, a nucleoprotein, phosphorus and no iodin. His iodothyroglobulin had the elementary composition C, 52.2; H, 6.7-6.96; N, 16.51-16.67; I, 1.57-1.75; S, 1.77-1.95; O, 20.85, and a molecular weight of about 8,000. It was difficultly soluble in water, soluble in neutral salts and very dilute

acetic acid, more easily in dilute alkali. On boiling with five per cent hydrochloric acid it split off much carbohydrate, which was not a pentose. The nucleoprotein contained carbohydrate radicals (not pentose), xanthin bases, and 0.16 per cent of phosphorus.

A pepsin digest of iodothyroglobulin yielded a substance resembling iodothyrin, with 5.27 per cent iodin. A trypsin digest completely dissolved the compound, the solution containing no iodin nor iodid, but much tyrosin, indicating that the iodin was not present originally in the tyrosin group. Decomposition with acids gave an "iodothyrin" residue; with concentrated acids iodin was liberated as iodid.

Iodothyroglobulin from different sources (glands of sheep, pigs, oxen, calves) has the same composition except for the iodin content (0–1.7 per cent). Iodothyroglobulin from children's thyroids has a low iodin content; that from a man dosed with potassium iodid was high. The compound amounts to about 10 per cent of the fresh gland (one-half to two-thirds of the dry tissue).

Further examination of prolonged digests with trypsin and with baryta led Oswald (*f*) (1909) to the conclusion that the iodin is united in the indolradical in the protein.

Blum (*c*) (1899) considered that iodothyroglobulin cannot be a definite compound since its iodin percentage varies. If, however, some one or more of the radicals of this protein have the power to unite with iodin, it is possible to conceive a variation in iodin content, and in iodin content only.

Wiener (1909) found from experiments on dogs that under normal condition the two thyroid lobes have approximately the same weight, contain the same amount of iodothyroglobulin, and the same iodin percentage. The iodothyroglobulin varies between 14 and 60 per cent of the weight of the dried gland. Feeding with sodium iodid increases the amount. Nürnberg (1909) confirmed the constant elementary composition. The hydrolysed contents include arginin, histidin, lysin, tyrosin, glutamic acid, glycin, alanin, leucin, phenylalanin, aspartic acid, and α-pyrrolidin carboxylic acid. Nürnberg considered that the iodin is probably united in the tyrosin or tryptophan radical. Koch (*a*) (*b*) (1911) confirmed the presence of histidin in the digest, and he subsequently (1913) tried to ascertain the nature of the iodin-containing-complex, using the Reid Hunt acetonitril test without success.

Marine and Feiss (1915) consider, from experiments on iodin absorption, that the elaboration of iodothyroglobulin is a slow and complex process.

In 1915 E. C. Kendall (*c*) (*i*) published the results of his first four years' work on the gland; in 1919 he was able to announce the isolation of a definite crystalline iodin compound, *thyroxin* (α-iodin), subsequently, with A. E. Osterberg, verifying the constitution of the compound and de-

tailing its chemical properties. The results of these three important papers are summarized below:

The starting point of the work was the discovery that hydrolysis with sodium hydroxid in alcohol yielded 75 per cent of the iodin in the gland in a dialysable condition, but still in organic combination. The digest contained two types of compounds, one soluble in acid, and another insoluble. The group of substances soluble in acids consisted chiefly of amino-acid complexes. The iodin compound in the group was precipitated to a large extent by mercuric sulphate, and almost quantitatively with silver sulphate and magnesium oxid, but was largely decomposed by this treatment. The iodin was easily split off by oxidizing agents. The group of substances insoluble in acids was acidic, had the general properties of a fatty acid, was easily soluble in dilute alkalis, and was reprecipitated by any acid. After removal of fatty acids and sulphur with petroleum ether the product contained four per cent of iodin. By repeated solution in alkali and precipitation with acid, and subsequent partial extraction with ethyl acetate the ester-soluble fraction contained 13-14 per cent of iodin. Further hydrolysis of this group of substances with sodium hydroxid at a high temperature split of lauric acid and tryptophan.

Similar cleavage was obtained by hydrolysing fresh thyroids with aqueous sodium hydroxid for 24 hours. The fats were removed as sodium soaps, and a clear alkalin filtrate of the hydrolysed thyroid proteins containing practically the entire iodin content was obtained. Acidifying this gave a fine flocculent precipitate, which, when dried, amounted to 0.1 per cent of the total weight of fresh gland, and contained 26 per cent of the total iodin, so that approximately three-fourths of the total iodin-containing compounds were soluble in acid, and only one-fourth insoluble. This proportion is constant at different times of the year and in different samples from different species, and is considered to represent the equilibrium existing in the gland between the completed specific iodin compound and the materials used for building it up.

The precipitate, heated to about 40° to 50° C. in aqueous suspension, changed to a black tarry mass, soluble in acid alcohol, and repeated precipitation with barium hydroxid from this solution gradually concentrated the iodin compound until it contained 47.3 per cent of iodin. This preparation was dissolved in 95 per cent alcohol, evaporated on a water-bath to dryness, and accidentally heated for an hour. The white residue was insoluble in alcohol and contained 60 per cent of iodin. About 200 mg. of *thyroxin* was obtained in this way; but preparation on the large scale proved impossible until various sources of error had been eliminated, which were: a deleterious effect of temperature during precipitation with acid; initial alkaline hydrolysis in all metal tanks except Ni, Au, Ag, and Pt breaks off iodin from organic combination; carbondioxid plays an important rôle in the separation of thyroxin from impurities, but the tem-

perature must be kept below 50-60 C.; the thyroxin content of different samples of desiccated thyroid varies as much as 400 per cent.

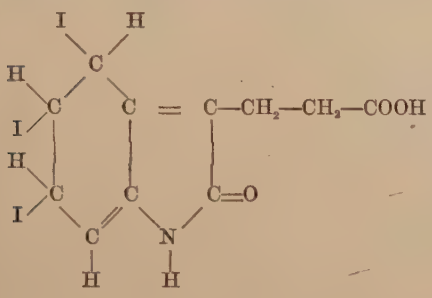
The present method in use is, according to Kendall (*i*) (1919), as follows: "The fresh thyroid glands are hydrolysed in 5 per cent sodium hydroxid in a nickel kettle, the fats are removed by rendering the sodium salts insoluble, and the clear alkaline filtrate is cooled and acidified. The acid insoluble constituents containing practically 100 per cent of the thyroxin present are filtered off. This material is redissolved in sodium hydroxid and reprecipitated, using hydrochloric acid. The precipitate is now air-dried and is dissolved in 95 per cent alcohol. The excess hydrochloric acid which remains in the air-dried precipitate is neutralized with sodium hydroxid until it is almost neutral to moistened blue litmus paper. A heavy, black, tarry precipitate forms, which may be removed by filtration. The alcoholic filtrate is treated with barium hydroxid by adding a hot, very concentrated aqueous solution of the hydroxid to the alcohol, and refluxing. The treatment with barium removes certain heavy dark impurities. A small amount of sodium hydroxid is added to the filtrate and carbon dioxid is passed through the solution. The barium and sodium carbonate are removed by filtration, and the alcohol is distilled. The last traces of alcohol are removed by heating in an evaporating dish. The aqueous residue is now acidified with hydrochloric acid. The precipitate is dissolved in alkalin alcohol, carbon dioxid is passed through the solution, the precipitated sodium carbonate is removed, and the alcohol evaporated. The last traces of alcohol are removed by heating on a water bath and the solution is allowed to stand. The monosodium salt of thyroxin will separate at this point. The yield is not quantitative, and it must be further purified by dissolving in alkalin alcohol, passing in carbon dioxid, distilling the alcohol, and allowing the monosodium salt to crystallize a second time. This may then be precipitated from an alkaline alcoholic solution by the addition of acetic acid. Resolution in alkaline alcohol and precipitation with acetic acid for five or six times removes the impurities and will yield thyroxin containing the theoretical percentage of iodin."

Writing in 1919, Kendall stated that 33 grams of the compound had been separated from 6550 pounds of fresh thyroid material, made up almost entirely of hog thyroid.

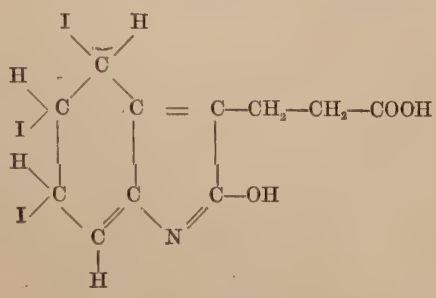
Thyroxin is stated to be 4-5-6-trihydro-4-5-6-triiodo-2oxybeta-indole propionic acid. It exists in three forms: (I) the keto form with the carbonyl group adjacent to the imino, (II) a tautomeric enol form, and (III) a form with an open ring structure (cf. creatin and creatinin). It can be regarded as a derivative of tryptophan. Kendall considers that the third form is that in which thyroxin occurs in the body.

The change to the open ring form is brought about very easily in the presence of certain substances which are amongst the products of the hydrolysed protein, and which contain the indol nucleus.

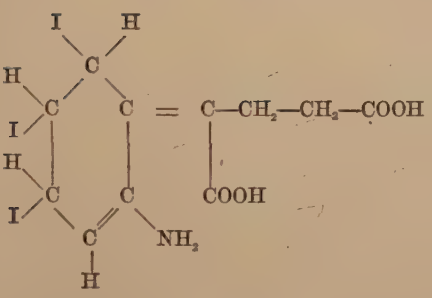
Thyroxin, as represented by formula (i) is a white, highly crystallizable substance (needles), odorless, and tasteless. It exists in this keto form in acid solution. It is insoluble in organic solvents except those strongly acidic or basic; it is soluble in alcohol in the presence of a mineral



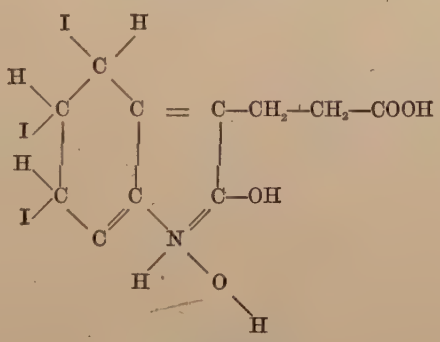
i. Keto form.



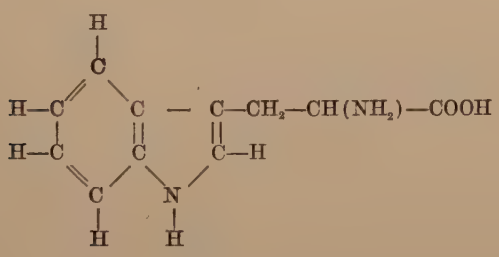
ii. Enol form.



iii. Open ring form.



iv. Amino-hydrate.



v. Tryptophan.

acid or an alkali. It is stable towards heat (m.p. about 250° C.), its molecular weight is 585, and the empirical formula $C_{11}H_{10}O_3NI_3$. It is amphoteric. Through the presence of the imino group it easily gives rise to salts: sulphate, hydrochlorid, a ureid (with HCNO), an acetyl derivative (with acetic anhydrid). These are all crystalline compounds. It yields crystalline mono-salts (Na, K, NH_4) and di-salts (Na, K, NH_4, Ba,

Ca, Mg, Ni, Zn, Cu, Cu), all so easily decomposed, even by boiling with water, that scarcely any can be prepared pure.

The enol form (II) exists in alkaline solution. It can be prepared by cold hydrolysis of the ammonium salt, solution in pyridin, and addition of water, when it separates in rosettes or sheafs of short needles with melting point 204°C. It is readily soluble in anhydrous or aqueous pyridin and quinolin and in formic acid. It easily changes to the keto form.

The open ring form (III) is obtained by adding sulphuric acid to an alkaline aqueous solution of thyroxin, removing the precipitate from solution, suspending in distilled water, and boiling. The thyroxin is precipitated in long bundle-blades, with melting point 225° C. It is soluble in alcohol, changing in solution to the keto form which separates.

An "amino-hydrate" form (IV) can be easily prepared by heating an alkaline solution of thyroxin, and adding 10 per cent ammonium chlorid. Fine branching crystals separate and the melting point is 216°C. If these are suspended in distilled water containing a small amount of formic acid, and the suspension boiled, the crystals are changed to the open ring form.

The most important property of thyroxin is evidently the ease with which one form changes to another. Kendall and Osterberg consider that the explanation of the peculiar properties of the imino-group in the pyrrole ring lies in the presence of the hydrogen atoms in the benzene ring, and cite anilin and hexahydroanilin in comparison. It seems much more likely that the hydrogen atoms, which are also present in tryptophan, have in themselves no effect, the effect either being traceable to the large-atomed halogen (as the authors also suggest; cf. also Kendall (*f*), 1918), or with the complete saturation of five of the carbon atoms in the benzene ring.

A convenient rough qualitative test for thyroxin is the addition of nitrous acid to an alcoholic solution or aqueous suspension in presence of hydrochloric acid. A yellow color is developed, which, on addition of ammonia, changes to deep red, and in dilute solutions pink.

Thyroxin is more susceptible to reduction than to oxidation. Zinc (or other metals except nickel), in alkaline or acid solution splits off iodin, and appears to break up the organic nucleus. Mild oxidizing agents have no effect. Stronger reagents break down the molecule. In weak alkaline solution it is very unstable to sunlight; iodin is split off as hypo-iodous acid, and subsequently as free iodin. This is considered to have a bearing on the physiological effect. Thyroxin does not rotate polarized light, but this does not necessarily indicate, as Kendall and Osterberg have maintained, the absence of an asymmetric carbon atom. A racemic mixture would also produce no effect. It is claimed that the keto form of thyroxin crystallizes in six distinctly different forms, but the published photographs of these suggest that five at least are slight variations due to slight changes in the

solution content. The iodin content is 65 per cent, the solubility one part in 84,000, keto form.

Osterberg is stated to have synthetized a small quantity of thyroxin in 1917 and efforts are at present being made in the Mayo laboratories to reproduce the synthesis on a larger scale.

Summing up, it would appear that only two definite compounds containing iodin have been isolated from thyroid tissue, a globulin (iodothyroglobulin) existing as such in the gland, and a derivative of tryptophan (thyroxin), obtained as a cleavage product, and containing 65 per cent of iodin. Thyroxin accounts for one-fourth of the total iodin content of the gland. Iodothyroglobulin has a variable iodin content ranging from a trace to 1.7 per cent. This iodin content varies with that of the gland and probably accounts for practically all of it; otherwise the compound has a definite composition. It has not yet been shown that thyroxin occurs amongst the cleavage products of the globulin, nor is any definite information available as to the form in which the remaining three-fourths of the iodin exists in the cleavage products.

Evidence Connecting the Iodin Compounds of the Gland with the Internal Secretion

General Discussion.—The internal secretion appears to leave the gland through vascular channels. Carlson and Woelfel (1910) showed that the rate of lymph production in normal thyroids is very small, but is much increased in goiters though no iodin is present. They criticize the earlier view that the colloid passes to the lymph spaces. Watts (1915) showed that nervous stimulation (cervical sympathetic) produces vasoconstriction in the gland, and this, together with decrease of blood flow produced mechanically, is accompanied by a decrease of iodin and water content, which are considered to leave through the vascular channels. Bensley's (*b*) results (1916) indicate that the secretion exists in the cells as a dilute solution resembling the colloid, and is probably excreted directly through the vascular channels. Marine and Feiss (1915) state that it is possible to wash out with defibrinated blood a very small amount of idothyroglobulin. On *a priori* grounds this seems very unlikely; it is to be expected that only simple compounds such as thyroxin will pass into the blood stream.

So far there is no definite test for the internal secretion of the thyroid. We are, in a measure, forced to test any preparation considered to be the internal secretion or its active ingredient indirectly by a comparison with desiccated thyroid itself, using as tests the action on goiter (which is also produced by various forms of iodin administration), the comparative toxic effect of large doses, the specific effect on myxedema and cachexia thyreo-

priva, which, outside of man, is particularly liable to misinterpretation, and on the influence on metabolism, which alone lends itself to any accuracy.

The acetonitril test of Reid Hunt is no longer considered specific for thyroid (Beebe, Olds, Lussky, Allen), while the hastened metamorphosis of thyroid-fed tadpoles, discovered by Gudernatsch (*b*) (*c*), and confirmed by many other workers, has been shown by Swingle to be produced also by inorganic iodin, by iodids, and by iodoform, and to be specific for iodin and not for thyroid. This throws doubt on experiments such as those of Marine and Rogoff (*b*), in which an attempt was made to ascertain the rapidity with which the intact gland elaborates its specific iodin compound, and in which the iodin test was used also (1916, also Rogoff and Marine).

The metabolic method available is the measurement of the increased excretion of the products of catabolism, especially phosphates and total nitrogen, which invariably follows upon the oral administration of fresh or desiccated thyroid, and which is usually accompanied by loss of body weight. There is some evidence that iodin increases phosphorus excretion, but that of nitrogen excretion is unaffected. A second method is probably available; thyroid feeding definitely diminishes the rate of growth in young white rats (Cameron and Carmichael), and at the same time causes hypertrophy of the organs concerned with increased metabolism, namely, heart, liver, pancreas, kidneys, adrenals, etc. (Hoskins, 1916, Herring), and this effect is specific as contrasted with iodids (Cameron and Carmichael).

It should be remembered in considering the following statements that thyroid gland, administered by way of the alimentary tract, will, like other similar tissue, be broken down to small unit compounds before absorption, and no such compounds as iodothyroglobulin will be absorbed into the blood-stream as such. Iodothyrin is that part of thyroid and of iodothyroglobulin that resists solution under pepsin digestion, while trypsin splits off three-fourths of the iodin from organic combination (Oswald, 1899). Diiodotyrosin, fed to animals, appears incapable of assimilation as such, and most of the iodin is split off and excreted as iodid (Abderhalden and Slavu, Oswald (*g*), 1910). No information is yet available as to the effect of digestive enzymes on thyroxin, but its physiological action is stated to be the same whether it be administered orally or intravenously.

Discussion of Individual Substances.—*Iodothyrin.*—This preparation has played such a considerable part in thyroid literature that it seems desirable to consider in some detail the evidence for and against its being the internal secretion of the thyroid. Baumann and Roos stated that it has all the characteristic properties of thyroid, with a more rapid physiological action than the fresh gland or tablets. Baumann and Goldmann stated that it prevents the appearance of cachexia thyreopriva in thyrodectomized dogs. This view is supported by Hildebrandt and Irsai and denied by Notkin (*b*), 1896, and Wörmser. Roos (1896), experimenting

on a dog, obtained a fall in weight, a rise in nitrogen excretion, and a doubtful rise in phosphorus excretion. Treupel obtained similar results in a case of myxedema, and with rabbits. (Cf. also Grawitz, v. Vamossy and Vas). Magnus-Levy stated that iodothyrin has as great an effect on the respiratory quotient as has thyroid. Hennig did not get constant positive results with goiter. Barbèra found that the physiological effects of iodothyrin are not the same as those of iodin or iodids. Asher and Flack found that they are not the same as those of thyroid. Falta (*a*) found that the physiological action of iodothyrin is much less than that of dried thyroid substance.

While different methods of preparation may account for part of this total lack of uniformity, it would seem certain that if iodothyrin does possess some physiological and metabolic activity, it does so to a very much less extent than thyroid itself.

Cyon and Oswald found that iodin-containing peptones and proteoses derived from thyroid have no thyroid action on blood pressure and heart beat, and do not possess the physiological properties of iodothyrin. Asher and Abelin (1917) have examined "Thyreo-glandol-Roche," a thyroid preparation soluble in water, free from protein, and containing little iodin, and stated that it exerted the same physiological and metabolic effects as the whole gland. Eiger (1917) obtained similar results with a liquid obtained by perfusing the gland with Ringer's solution, and free from protein, iodin, and cholin. According to Strouse and Voegtlin diiodotyrosin has no similar metabolic or physiological effect to thyroid, and no curative effect on myxedema and cretinism.

Iodothyroglobulin.—Oswald (1899) quotes Magnus-Levy as authority for the cure of myxedema by iodothyroglobulin. Administration to a dog increased the nitrogen excretion, while the phosphorus containing nucleoprotein had no effect (Oswald, 1902, Courvoisier and Lanz). It has the specific thyroid effect on blood pressure and pulse (Oswald, 1901). Pick and Pineles, using the effect on cachexia thyreopriva as a test, find that iodothyroglobulin resembles thyroid, and iodothyrin does not. More recently, Oswald (*i*) (1916) has studied the physiological properties more exactly. Iodothyroglobulin and its methylene derivative closely resemble thyroid. Iodothyrin, gorgonin, and spongin show similar but weaker activity, iodocasein, iodotyrosin, and thyroid nucleoprotein no effect.

Thyroxin.—Kendall (*h*) (1919) finds physiological effects after injection of thyroxin similar to those of thyroid. Heavy single doses are not fatal, while continued smaller doses prove fatal (goats). Thyroxin increases the basal metabolic rate. Plummer has shown that 1 mg. given an adult weighing 150 lbs. increases the rate 2 per cent. Kendall considers that thyroxin acts as a catalyst, the activity being due to the CO-NH group. It relieves all the symptoms of cretinism and myxedema to the same extent as does desiccated thyroid (1918). Janney (*a*) found that with normal in-

dividuals the nitrogen excretion was increased, and physiological symptoms appeared similar to those produced by overdoses of thyroid. This same observer made a detailed investigation into the comparative effects of orally administered thyroxin and thyroid in thyroid diseases and found that the therapeutic effect of thyroxin is unchanged by passage through the gastro-intestinal tract. The test of decrease in growth-rate and hypertrophy of body organs (rats) has now been applied to thyroxin, which gives results similar to those obtained with thyroid itself; this affords an additional rigorous proof of the identity of thyroxin with the essential chemical compound secreted by the gland. (Cameron and Carmichael, 1921.)

While iodothyroglobulin produces physiological and metabolic actions resembling those produced by thyroid, in some respects these do not appear to be much greater than those produced by other organic iodin compounds or complexes such as gorgonin, spongin, etc. These effects are, it must be remembered, produced after passage through the alimentary tract where hydrolysis takes place and some smaller iodin compound is actually absorbed. On the other hand thyroxin appears to produce all the specific effects of thyroid, in a degree bearing some relation to the relative iodin content, and this whether injected directly into the blood stream or given through the alimentary tract. On *a priori* grounds the active part of the thyroid secretion should consist of a relative simple compound of this nature. The whole mass of evidence leads to the conclusion that thyroxin is one of the active compounds secreted by thyroid. Before it can be definitely stated that it is the only specific compound, it is necessary to know more of the hydrolysed products containing 75 per cent of the iodin in the gland, soluble in acids, of amino-acid nature, and which, according to Kendall (1915) possess some physiological activity.

The Relationship Between Iodin Content and Thyroid Activity.—It was shown by Roos (*e*) (1899) that thyroid glands rich in iodin content produce greater increase in nitrogen excretion and greater loss of body weight than those poor in iodin, while "iodin-free" glands (i. e., containing too small an amount to be detected by Baumann's method of analysis) produced no effect. Fonio (1911) also found that the increase in nitrogen excretion is proportional to the iodin content of the thyroid fed, and Poillon (1916) obtained the same result. Heavy doses of iodin-rich thyroid are more toxic than corresponding doses of a thyroid containing less iodin (Stoland, 1912). The metabolic and physiological activity of iodothyroglobulin is proportional to the iodin content (Oswald, 1902, 1916, Lanz).

The connection between iodin content and thyroid activity has been so widely accepted that certain pharmacopeias require a definite iodin percentage. Van Os reports adversely on this method of standardization.

Cameron and Carmichael (1920) found that the decrease in rate of

growth in young white rats fed a hog-thyroid preparation containing 0.34 per cent of iodin is definitely greater than in rats of the same litter fed a sheep-thyroid preparation containing 0.18 per cent of iodin, and have obtained some evidence that the degree of hypertrophy of heart, liver, kidneys, etc., which results from such feeding is proportional to the iodin content of the thyroid fed.

Assuming that thyroxin is the essential constituent of the secretion, and results from the passage of thyroid through the alimentary tract, since Kendall has shown that in thyroid it bears a definite relation to the total iodin content, it follows that thyroid activity must be directly proportional to iodin content.

The Chemistry of the Pathological Thyroid Gland

Few comparative observations have been made on the chemical composition of the normal and pathological gland, with the exception of those connected with iodin. Cholesterol was, according to Bubnow, found in a struma-cyst by Scherer (1843) and by Kletzinsky (1852). Reinbach claimed to obtain a specific sugar from a colloid goiter; the melting point of the osazon was 193°C. Goitrous glands contain relatively more silica than normal (0.043 Si as compared with 0.017, Schulz). From an analysis of Morgenstern's figures it was found that goitrous glands contain magnesium, apparently an abnormal constituent, and their calcium, phosphorus, and chlorin figures are possibly slightly higher than normal.

Baumann (1895) noted that goitrous glands contain proportionately less iodin, but Oswald (*a*) (1897) showed that the total amount in such glands is not below normal. Hunziker considers that goiter amounts to a fundamental hypertrophy of the thyroid caused by the effort of the organism to make up for a deficient iodin supply; with this may be connected Seidell and Fenger's observations on cattle thyroid enlargement in cold weather and the apparently inverse ratio which exists between iodin percentage and size of thyroid even with normal glands of the same species. Marine and his co-workers have devoted much attention to the amount of iodin present in pathological glands. Marine and Lenhart find that the iodin content varies inversely with the degree of hyperplasia. The rapidity with which iodin is taken up by the gland depends on the degree of active hyperplasia. Exopthalmic goiter is constantly accompanied during the progressive stages by thyroid hyperplasia, the iodin content varying inversely with the degree of hyperplasia. In endemic cretinism and myxedema there is a very low iodin content.

Pellegrini (*a*) (1915) states that the amount of iodin does not depend on the state of nutrition. There is an increase above the average in cases of sudden death, cirrhosis of the liver, and acute inflammatory processes

of the intestine, a decrease in tuberculosis, anemia, inflammation of the lungs, pellagra, and chronic inflammatory processes of the intestine, but in all cases individual variations are great. Zunz's observations are interesting and his results are worthy of study.

Iodothyroglobulin from colloid goiter does not differ from that prepared from normal glands except for its lesser iodin content, whence its metabolic effects are slighter (Oswald, 1901, 1902, 1).

Wilson and Kendall (1916) obtain results similar to those of Marine and Lenhart. Hyperplastic glands show, in the early stages, a fall in iodin percentage and total iodin content, which lessens with the regression of the hyperplasia, hence it seems probable that the total amount of iodin in the entire gland in hyperplastic goiters with very advanced regressions averages more than the total amount in non-hyperplastic cases. Adenomas and carcinomas show low iodin percentages. Thyroxin is present in the actively hyperplastic glands of exophthalmic goiter to a much smaller extent than in normal glands; this is interpreted as the result of its greatly increased diffusion from the gland into the blood stream.

General Conclusions

The evidence available indicates that the thyroid gland differs chemically from other glands chiefly in its power of retaining iodin and elaborating one or more specific iodin compounds. One of these, iodothyroglobulin, exists as such in the gland, and may amount to as much as 50 per cent of the dried tissue. Amongst the cleavage products of thyroid and probably of iodothyroglobulin occurs thyroxin, stated to be 4-5-6-trihydro-4-5-6-triiodo-2-oxybeta-indolepropionic acid, containing 65 per cent of iodin, and closely related to tryptophan. It is interesting to note that earlier workers generally considered that the iodin was contained in the tryptophan or some similar radical, though it was reserved to Kendall to isolate the actual compound. The total thyroxin present in the gland contains only one-fourth of the total iodin, and there is as yet no information as to the form of combination of the remaining three-fourths, except that it is organic. The maximum amount of iodin observed in dry thyroid tissue is 1.16 per cent; the corresponding maximum thyroxin content is therefore 0.44 per cent, and the ordinary content can be considered as between 0.05 and 0.15 per cent. Thyroxin has not yet been shown to exist as such in the gland, but it produces all the physiological and metabolic effects of thyroid tissue, and on *a priori* grounds the essential constituent of the secretion would be expected to consist of some such compound.

While it is doubtful if the thyroid secretion is absolutely essential to normal adult individuals, especially herbivora, its chief general effect is undoubtedly to stimulate the general metabolic activity (Easterbrook, von

Bergmann, Carlson and Jacobson, Yushchenko, 1911, Kendall, 1919), and the theory of detoxication put forward by Blum (*a*) in 1898, and by Blum and Grützner in 1914, and other workers at various times, can no longer be regarded as tenable. It is tempting, however, modifying Grobly's idea, to link this with the metabolic activity of the secretion, and to consider that under normal conditions iodin is gradually built up into the iodothyroglobulin structure as it becomes available from the blood stream (primarily, from the diet), the radical concerned being that of thyroxin, derived from tryptophan, that iodothyroglobulin is the non-toxic storage form of iodin, and that thyroxin is gradually liberated into the blood stream by the breaking-up of iodothyroglobulin within the gland, normally at such a slow rate that no toxic effects are produced.

It may be hoped that, at an early date, much fresh light will be shed on the chemical problems of the thyroid. When we know the relationship between iodothyroglobulin and thyroxin, the properties of thyroxin derivatives containing other halogens, or with the halogen replaced by hydrogen, and the nature of the other organic iodin compounds which occur amongst the cleavage products, it will be easier to propound theories which will reasonably account for the chemical changes in the gland by which the internal secretion is produced, and for the mechanism by which it produces its physiological and metabolic effects.

The Pathological Anatomy and Histology of the Thyroid

. . . . . *David Marine*

Classification—Introduction—The Normal Thyroid—Hypertrophies and Hyperplasias—Regeneration—Colloid Glands—Atrophies—Degeneration—Inflammations—Tumors—Complications—Developmental Defects and Anomalies.

The Pathological Anatomy and Histology of the Thyroid

DAVID MARINE

NEW YORK

Introduction

The thyroid gland is one of the oldest and most constant organs of Chordates. It exists as the "endostyle organ" in the lowest of Chordates—the Tunicates, in Amphioxus and in Ammocœtes (larval lampreys). Owing to a curious biological preservation the Ammocœte combines in its life cycle both the endostyle organ and the ductless thyroid. The dis-

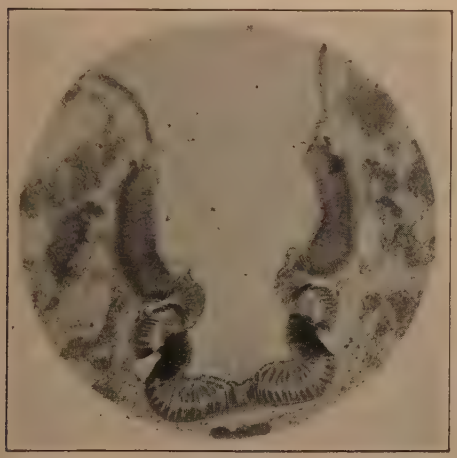


Fig. 1. Cross section of endostyle organ of Holocynthia johnsonii with adjacent parts of branchial (pharyngeal) sac. (After Marine, Johns Hopkins Hosp. Bull., 1913: 24.)

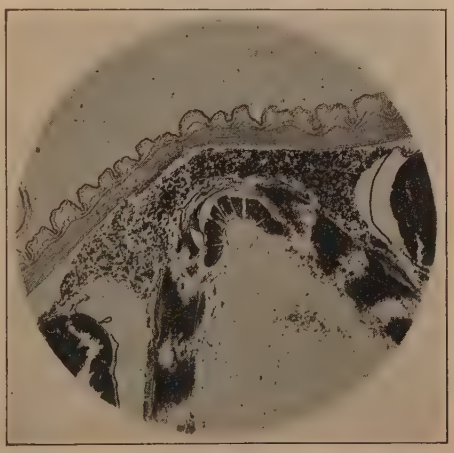


Fig. 2. Cross section of endostyle organ of Amphioxus calif., showing its relation to branchial (pharyngeal) sac and gill filaments. (After Marine, Johns Hopkins Hosp. Bull., 1913: 24.)

appearance of the endostyle and the development of the ductless thyroid alveoli from definite groups of cells of the endostyle has been carefully studied during the metamorphosis of the Ammocœt (see Figs. 1, 2, 3, 4). We are at present concerned only with the ductless thyroid. Morphologically it is one of the simplest of body tissues and resembles more closely

Fig. 3. Cross section of the endostyle organ of Ammocœtes branchialis taken through its duct. (After Marine, Johns Hopkins Hosp. Bull., 1913: 24.)

the lung than any other tissue. Indeed, there are many interesting embryological, anatomical, physiological and pathological relations between the thyroid and the lung which have added much to our knowledge of the physiology of inter-relationships. The thyroid tissue is one of the most labile tissues in the body, capable of rapid overgrowth and of rapid involution. Its wide range or cycle of morphological changes makes it possible to detect easily morphological changes which, if interpreted in terms of function, are but little removed from normal, but which, if interpreted in relation to similar morphological changes of other body tissues less well endowed with the capacity for growth, have frequently resulted in too great importance being attached to the pathological anatomy.

The outline of human thyroid changes given at the beginning of this article combines in sequential order so far as possible, the physiological

Fig. 4. Cross section of the thyroid area of Ammocœtes branchialis in the last stages of metamorphosis showing well formed thyroid alveoli together with considerable unabsorbed cell detritus and pigment from the old endostyle organ. (After Marine, Johns Hopkins Hosp. Bull., 1913: 24.)

relations with the anatomical changes. There are no essential anatomical changes in the thyroid that have not their counterpart in other tissues, hence the major groups will be recognized as the accepted groupings of anatomical changes common to all body tissues. Brooks, Dohrn, Ferguson, Gudernatsch (*a*), Hermann and Verdun, His (*a*), Kastschenko, Kingsbury, Mall, Marine (*b*)(*c*) Müller, A., Müller, W., (*b*), Reese, Schneider, Stieda, Stockard.

The Normal Thyroid

A definition of the normal thyroid, both gross and microscopic, is obviously the most essential and the most difficult feature of a description of its pathological changes. Since one's conception of the abnormal depends upon his conception of the normal, it seems desirable to outline briefly the salient features of the normal structure as they appear to the author. (See Figs. 5, 6, 7, and 8.)

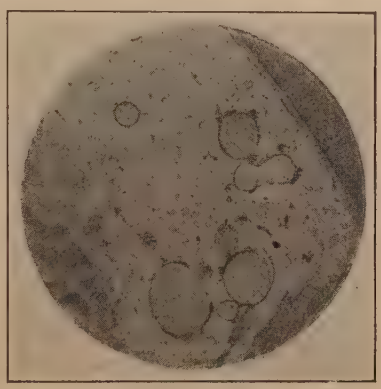


Fig. 5. Normal thyroid of bony fish (Salvelinus fontinalis) composed of scattered, rounded alveoli. The relation of the alveoli to bone, cartilage and muscle is shown. (After Marine and Lenhart, J. Exper. Med., 1910: 12.)

All anatomists have recognized the difficulty of defining the limits of normal. This is due to the great range of structural variations dependent upon variations in function. Such variations in structure as are dependent upon season, climate, geographical location, age, sex, food, state of nutrition and many others have not been fully discounted in the published descriptions. Studies in the chemistry must be correlated with the anatomical studies. In our experience a thyroid that has less than 0.1 per cent iodin cannot be normal anatomically, and a thyroid that has continuously had an iodin store above 0.1 per cent cannot be abnormal anatomically. The normal human adult thyroid weighs between 20 and 25 grams and does not exceed 0.35 gram per kilo. of body weight. The lateral lobes are in general symmetrical, the right lobe is usually slightly larger than the left. The isthmus is rarely absent, while the pyramidal portion is highly variable as regards its presence, shape and size. The strictly normal isthmus is a band of thyroid tissue one to two centimeters in width and one-half to one centimeter in thickness connecting the lobes in front of the trachea at the level of the third and fourth tracheal rings. The numerous departures from this normal type or the presence of a pyramidal process of variable size, is due to the failure of this portion of the thyroglossal tract to undergo absorption which normally takes place in early fetal life, but which, under the stimulus

of physiological need, persists. The entire gland is invested with an outer fibrous areolar capsule which strips easily, leaving a slightly

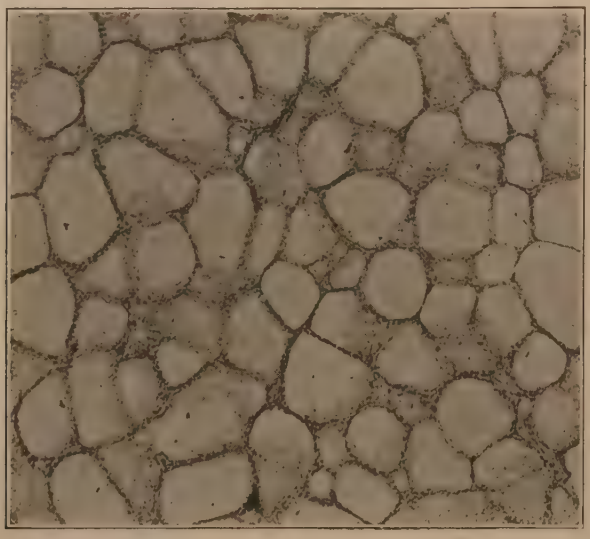


Fig. 6. Normal thyroid of common fowl (Gallus domesticus).

lobulated smooth surface. The inner or proper capsule is thin and translucent. Thickened portions of the true capsule (trabeculæ) extend into the gland and vaguely mark out the lobules and support the blood and lymph vessels. The color of the thyroid is similar in all animals examined and varies from a pale translucent amber-red to a bright amber-red. The consistency is firm and somewhat elastic. On section, the larger alveoli can be distinguished with the naked eye in all the larger mammals. They vary considerably in size, although the alveoli of normal thyroids vary the least and measurements of from 0.1 to 0.5 mm. would include most of the alveoli of the normal human thyroid. All the alveoli are filled with a glairy amber-colored viscid globulin—the so-called colloid—which gives to the thyroid its specific characteristic, chemical and physical. This colloid contains the active principle of the gland—an iodin compound which Kendall isolated in pure form and named thyroxin and it is believed to be the only vehicle for storing this very active substance in an inert manner.

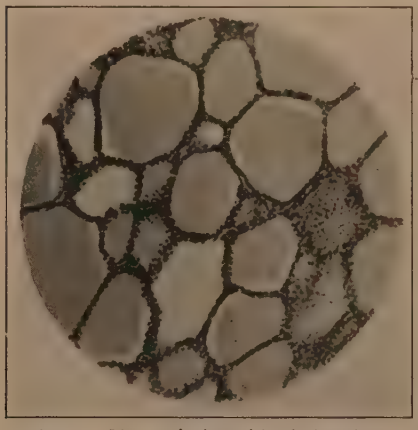


Fig. 7. Normal thyroid of the sheep. (After Marine, Johns Hokpins Hosp. Bull., 1907: 18.)

The microscopical appearance of the thyroid unit—the alveolus, is similar in all animals from fish to man. The alveoli are in general round or oval, closed spaces lined with a single layer of low cuboidal, or at most cuboidal epithelium. (High cuboidal or columnar epithelium always indicates hypertrophy.) The cells are quite regular in size, although one can often distinguish the so-called chief and colloid cells. They probably represent different stages of secretory activity. The nuclei are small, basal and vesicular. The colloid lies in contact with the free border of the epithelial cells and completely fills the alveolus save for occasional vacuole-like areas. It is homogeneous and stains deeply with acid dyes. The colloid of adjacent alveoli varies in consistency and in staining intensity. The blood and lymph capillaries form richly anastomosing networks about each alveolus and come into very close relation with the lining epithelium. In the human thyroid, particularly in early life, there are groups of undeveloped thyroid cells —the so-called "thyroid rests" lying in the stroma between the developed alveoli. There are normally lymphoid cells in the stroma and under conditions of generalized lymphoid hyperplasia, as in myxedema, exophthalmic goiter, Addison's disease and status lymphaticus these foci may undergo marked hyperplasia. Anderson, Arnold, Bartels, R. R. Bensley (*a*), Cavatorti, Cowdry, Flint, Forsyth (*a*), Francois-Frank and Hallion, Kölliker, Langendorf, Lindemann, Major, Matsunaga, Norris (*a*), Rhinehart, Schmidt, Simon, Stewart, Streiff.

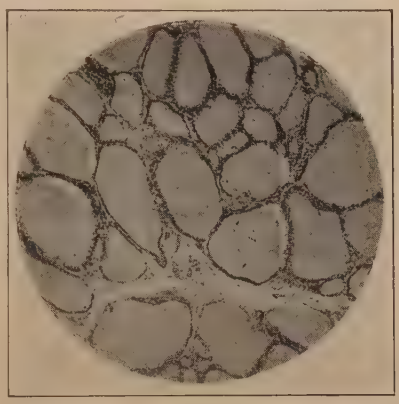
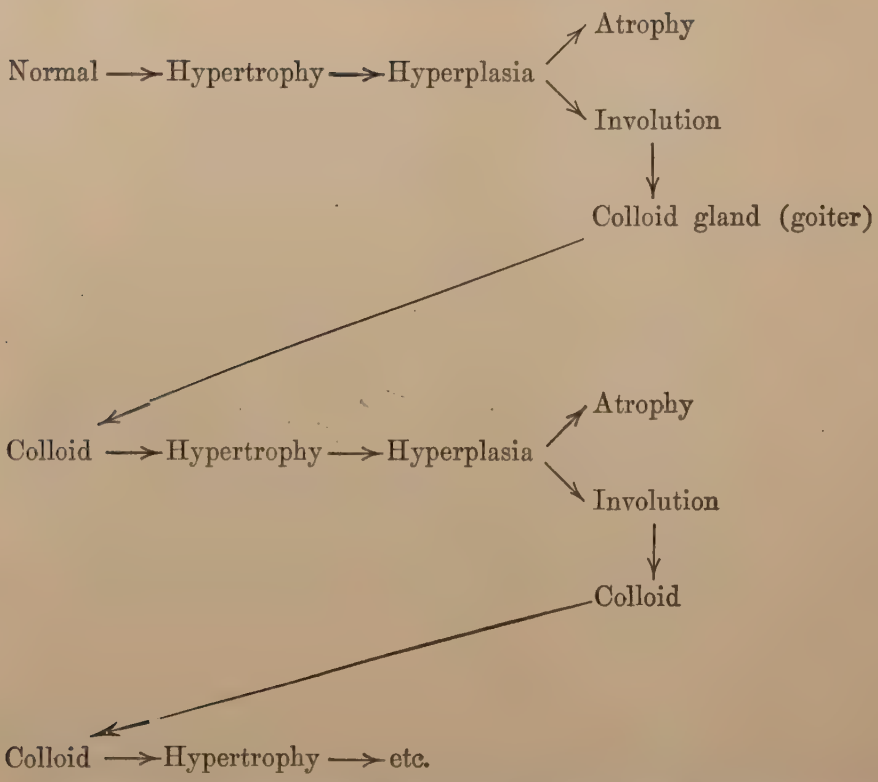


Fig. 8. Normal human thyroid showing trabecula and its relation to stroma.

Hypertrophies and Hyperplasias

This group comprises the developmental and growing stages of all goiters irrespective of their clinical associations both in man and in the lower animals, in simple goiter, in exophthalmic goiter and in myxedema and cretinism. Hypertrophy and hyperplasia represent different degrees of the same process. They must be considered together, although technically, hypertrophy may be said to end when cell proliferation begins. The proper physiological and sequential relation of these changes is simple, although in human goiter there are many secondary and complicating variations in morphology that have led to controversy and confusion. This relationship of hyperplasias to the normal, atrophic and colloid thyroid is shown in the following scheme: Marine and Lenhart (*f*) (*g*), Carlson, Hesselberg, Pflug, Zielinska. (See Figs. 9 to 14.)



Whenever the iodin store of the normal thyroid falls below the normal minimum (0.1 per cent) the gland undergoes changes characterized by a general increase in its blood supply, a general decrease in the stainable colloid, and a general change from cuboidal to columnar epithelium. If these changes continue to the stage of cell proliferation it is properly designated as hyperplasia. There are all degrees of cell growth from the slightest departure from normal (hypertrophy) to the most marked proliferations (hyperplasia). The great majority of all glands showing hypertrophy and hyperplasia never proceed to the stage of clinical detectability as indicated by visible enlargement or by any symptom complex. Clinically, therefore, goiter must be considered relatively rare, while histologically it is extremely common. Hyperplasias may be classified as follows:

1. **Primary, that is, developing on a normal gland basis.**
   Developmental stage (compensatory).
   Involutionary stage (physiological recovery).
   Atrophic stage (physiological exhaustion).
2. **Secondary, that is, developing on a colloid gland basis.**
   Developmental stage.
   Involutionary stage.
   Atrophic stage.

Primary Hyperplasias.—*Developmental stage.*—Tracing the development of hypertrophy and hyperplasia from the normal gland, the first change noticed in the thyroid is a marked drop in the iodin store, usually below 0.1 per cent. This is associated with a decrease in the stainable colloid. The blood supply to the gland is increased, the capsule vessels dilate, hypertrophy and become tortuous. The capillary network about the alveoli also shares in the dilatation and hypertrophy. The gland becomes larger, softer and takes on a brighter red color. Microscopically, there is a lessening of the stainable colloid which at first manifests itself by a paler stain, later by vacuolization, and finally by the actual disappearance of the true colloid—its place being taken by a thin albuminous fluid, which when coagulated has the appearance of granular albuminous débris. As this colloid gradually disappears from the alveolus, the epithelial cells change from the low cuboidal to columnar and, finally, to high columnar. With the disappearance of the colloid and with the growth in size and number of epithelial cells, the color of the gland changes from the normal translucent amber-red to reddish translucency, to grayish-red and finally to the soft fleshy gray-red and opaque color of the marked hyperplasia. As the hyperplasia of the epithelial cells take place, the alveoli at first enlarge, later (to some extent due to the restraining influence of the capsule), infoldings and plications of the lining epithelium begin to appear. These infoldings may become so extensive as to fill the space formerly occupied by the colloid. The gland capsule and stroma also show hyperplasia roughly parallel with the epithelial proliferation and increased blood supply. In the active stages of hyperplasia the stroma increase is not prominent, while in the late or

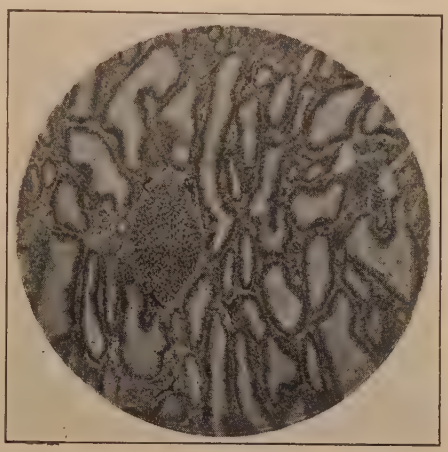


Fig. 9. Active hyperplasia thyroid of bony fish (Salvelinus fontinalis) illustrating the vascularity and alveolar distortions. (After Marine and Lenhart, J. Exper. Med., 1911: 13.)

Fig. 10. Active hyperplasia, marked degree, in thyroid of bony fish (Salvelinus fontinalis) giving papillary effect. (After Marine and Lenhart, J. Exper. Med., 1911: 13.)

exhaustive stages, and especially in exophthalmic goiter, the stroma may become strikingly prominent (this will be discussed more fully under Atrophies). Brissaud, Erdheim (*a*), Farner.

Involutionary or Recovery Stage.—Involutionary or recovery changes may begin at any stage of the hyperplasia. They may occur spontaneously or may be markedly hastened by the administration of iodin. The end stage of involution is the colloid or resting thyroid (this will be discussed more fully later). The process of involution may be arrested at any stage and active hyperplasia begin again. We must recognize all degrees of this regressive or involutionary stage from the marked hyperplasia back to the colloid gland, just as one must recognize all degrees of the progressive or actively hyperplastic change from the normal or colloid gland up to marked hyperplasias. The anatomical changes are, therefore, the reverse of those described under "Developing Hyperplasias," and are briefly as follows: The gland as a whole becomes firmer to the touch. The color changes from gray-red and opaque of the marked hyperplasias to gray-red and translucent, to reddish translucency and finally to the translucent amber-red of the colloid or resting stage. The blood supply diminishes. This is associated with a lessening of the caliber of both the arteries and veins due to a thickening of the vessel walls similar to that observed in the involuting thymus or uterus. The alveoli become visible to the naked eye. They appear as enlarged, rounded, highly variable sized cavities containing colloid. The colloid at first but palely staining and granular, gradually becomes more uniform, more dense, stains more intensely and finally comes to resemble in all respects the colloid of the normal thyroid. Paralleling the colloid accumulation, the high columnar epithelium with its infoldings and plications slowly returns to columnar, to cuboidal and finally to flat cuboidal if the involution is complete, while the infoldings take on more of the appearance of small tufts of stroma jutting into the alveolar space and covered with the prevailing type of alveolar epithelium. The stroma becomes less prominent either by compression or absorption, and when the gland returns fully to the colloid state, the

Fig. 11. Moderate active hyperplasia, thyroid common fowl (Gallus domesticus) illustrating the disappearance of colloid and the infoldings of the high columnar epithelium.

stroma may show hyaline transformation. As a rule this series of changes is associated with a considerable lessening of the size of the gland and always with a marked increase in the iodin store. Müller, L. R.

Exhaustion Atrophy.—Brief mention may be made of atrophies at this time because of the necessary physiological connection between the hyperactive and the exhaustive stages, though this will be more fully described under "Atrophies." While involution or recovery is the usual mode of termination of active hyperplasias of whatever clinical association and exhaustion atrophy the rare and unusual, it is of as great importance for the proper appreciation of the cycle of cell changes. Exhaustion atrophy is frequently seen in the marked hyperplasias of young animals and of children with myxedema and in the late stages of exophthalmic goiter. If hyperplasia and hyperactivity are allowed to continue without periods of physiological cell rest, the cells sooner or later die of exhaustion. The most characteristic morphological changes occur in the epithelium of the alveoli and in the stroma. At first the stroma is probably only relatively increased, but later there may be an absolute increase. The epithelial cells are in the early stages of the process high columnar in type, with here and there an atypical cell mass. As the atrophy progresses the epithelial cells become more variable in size, shape and staining reactions. The cells lose their uniform arrangement in the alveoli and piling up, desquamation and disintegration may be seen in the same alveolus with mitotic figures. All the cells of a given alveolus are not uniformly involved. The nuclei of involved cells show great irregularity, sometimes enlarged and hyperchromatic and always variable in size, shape and staining intensity. The colloid is markedly reduced or absent. As the atrophic process continues the alveoli are further reduced in size by cell death and advancing sclerosis until they may appear as compressed nests of cells without the outlines of alveoli. This change has been mistaken for carcinoma. Ewald, O. (*a*), Kocher, T. (*i*), Lewis, Meroz-Tydman.

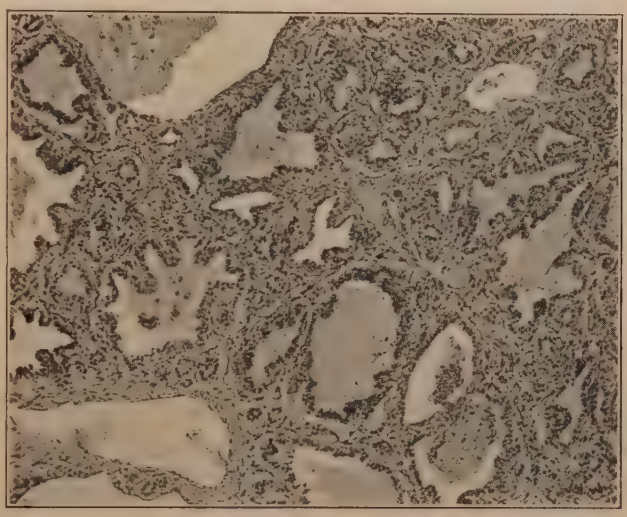


Fig. 12. More advanced active hyperplasia, thyroid of common fowl (Gallus domesticus) showing greater infoldings and variations in size of alveoli.

Secondary Hyperplasias.—*Developmental Stage.*—Secondary hyperplasias or active hyperplasias developing from the colloid or resting thyroid are illustrated clinically in the so-called secondary exophthalmic goiters, the thyroid enlargements developing in succeeding pregnancies, or finally in any thyroid which has undergone hyperplasia and involution more than once. Active hyperplasias developing from colloid glands are not essentially different from those developing from normal glands. Their interpretation offers more difficulties on account of the wider range of possible morphological changes and a more complicated life history. Thus it is unusual to find secondary hyperplasia uniform throughout a gland while with primary hyperplasias this is the rule. The reason for this lies in the fact that the thyroid is so frequently the seat of degenerative changes, hemorrhage, cyst formation, and so readily modified by trauma, by treatment, pregnancy, locality, intercurrent diseases, food, etc. Marine and Lenhart (*d*).

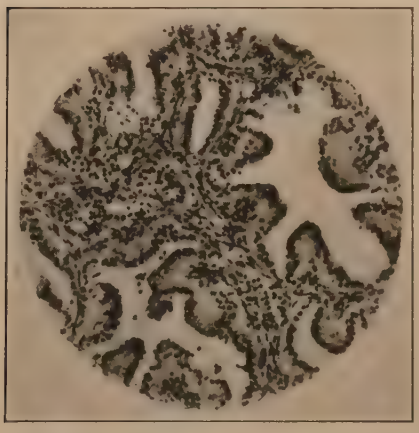


Fig. 13. Simple marked active hyperplasia, thyroid of sheep, marked infoldings and plications, very high columnar epithelium. (After Marine, Johns Hopkins Hosp. Bull., 1907: 18.)

The important anatomical changes are, however, similar to those occurring in the primary hyperplasias and are found in the blood vessels, the colloid, the epithelium and the stroma. The blood supply is increased. The stainable colloid is lessened, but slightly in the milder degrees, while it may be entirely absent in the marked degrees of hyperplasia. The epithelium changes from cuboidal to high cuboidal and finally to high columnar. These changes are not uniform throughout the gland and much confusion has arisen on this account. The hyperplasia is markedly influenced by the blood supply. The blood supply, as a rule, is best preserved in the subcapsular zone, and it is in this zone that the most marked hyperplastic changes are seen. Frequently one sees large central areas, or it may be but a few alveoli that fail to join in the

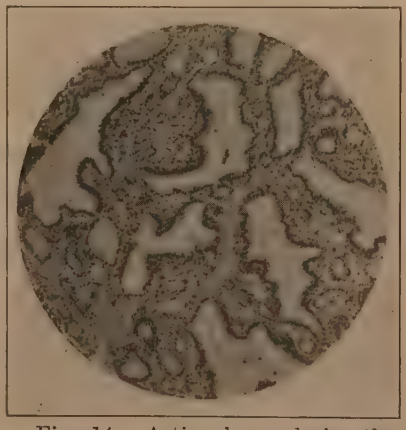


Fig. 14. Active hyperplasia, thyroid of man, illustrating the irregular size and distortion of the alveoli, reduced colloid, high columnar epithelium and increase in stroma. (After Marine, Johns Hopkins Hosp. Bull., 1907: 18.)

active hyperplasia. This variability is best explained by variations in the blood supply as has been demonstrated experimentally in the regeneration following partial removal. Ribbert (*c*), Roussy and Clunet (*b*) (*c*) (*d*), Virchow (*b*).

Involutionary or Recovery Stage.—The growth of a secondary hyperplasia may be arrested at any stage of its development and partially or completely return to the colloid or resting state again, just as in the case of the primary hyperplasias. The anatomical changes in this process are again the reverse of those seen in the developmental stage and identical with those outlined under "Involution of Primary Hyperplasias." The involutionary changes, however, are not so easy of recognition nor so easily interpreted because of the frequency of the several complications above mentioned to which the thyroid is so liable. MacCallum (*b*).

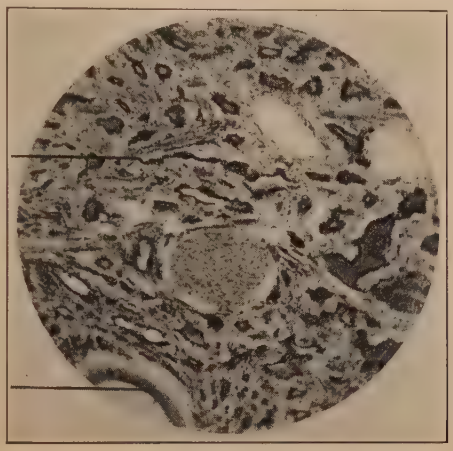


Fig. 15. Exhaustion atrophy, thyroid of bony fish (Salvelinus fontinalis). This particular fish had a large goiter and the figure is the representative picture of its microscopic appearance. Note the marked fibrosis, the compressed and distorted alveoli. The epithelium is high, columnar and irregular. (After Marine and Lenhart, J. Exper. Med., 1910: 12.)

Exhaustion Atrophy. — The secondary hyperplasia may undergo involution and recovery which is the common mode of termination, or, it may go on to exhaustion atrophy if the hyperplasia is permitted to continue without a period of physiological rest. The series of changes are similar to those already described as occurring in the exhaustion stage of primary hyperplasia. Obviously it is even less frequently observed because of the greater amount of thyroid tissue with which to compensate. Simmonds (*c*), Werdt (*a*), Wilson, (*a*) (*b*) (*c*).

Regeneration

(Compensatory Hyperplasia)

Regeneration and simple or spontaneous hyperplasia of developing goiters are identical anatomically and probably physiologically. The thyroid gland is one of the best adapted of mammalian tissues for the study of regeneration. If any differentiation between regeneration and spontaneous hyperplasia were possible it would be to restrict the term regeneration to the cell growth following the partial removal or partial destruction of the

gland. Some observers have stated that regeneration following partial removal ceases when the gland reaches its normal volume. This is not necessarily the case. The amount of thyroid normally needed by the organism cannot be measured quantitatively for the reason that the smallest number of thyroid cells capable of performing the thyroid functions under favorable conditions of environment and nutrition is much smaller than the number of thyroid cells required by the organism under unfavorable conditions. In short, the amount of thyroid depends on the physiological requirements of the animal, and this may be altered by a variety of means.

The histological characteristics of regeneration are identical with those described under hyperplasias. If one removes three-fourths of the thyroid of a dog or cat and rigid precautions are taken to prevent the animal's coming in contact with iodin, a series of changes takes place characterized by a striking decrease in the iodin store, the disappearance of colloid, an increase in the blood supply and a change in the alveolar epithelium first recognized in the subcapsular zone of the gland, in which the cells change from low cuboidal to cuboidal, to columnar and finally to high columnar with infoldings and plications. The rapidity of the process depends on the known factors of species of animal, age, the amount of gland removed, the presence of iodin and probably on the other factors of the nature of chemical coordination. Regeneration is not necessarily a part of the normal growth of a normal gland, as can be demonstrated in young animals, where the gland increases in size with the growth of the animal without in any way departing from normal chemistry or normal histology. Edmunds (*c*), von Eiselsberg, Eppinger and Hofer, Halsted (*a*) (*b*), Ribbert (*a*), Roussy and Clunet (*d*), Loeb (*b*), Weiner.

Colloid Glands (Goiters)

The colloid or resting thyroid may be defined as that anatomical and chemical state which is present when an active hyperplasia, primary or secondary, ceases further growth and returns to the condition nearest normal that such a gland can assume. Colloid glands (goiters) are normal physiologically and abnormal anatomically. They differ from the normal gland only in size and in showing the vestiges of previous active hyperplasia. Colloid glands are properly designated involutions or physiological atrophies of hyperplasias, and are capable of all the biological reactions of the normal thyroid in so far as these are at present known. Clinically, just as in hyperplasias, the great majority of colloid glands never reach the stage of clinical detectability. They complete the cycle of cell changes before sufficient enlargement has taken place and without any detectable symptoms. Unfortunately, many writers use the term colloid gland (goiter) as a clinical term synonymous with simple or endemic goiter. This is wrong.

It is properly an anatomical term. Colloid glands (goiters) may be present in association with several clinical complexes, most frequently in simple or endemic goiter and in exophthalmic goiter. In the older literature colloid glands (goiters) were designated "colloid degenerations" and "cystic degenerations." They have nothing in common with degeneration as this term is at present used. The opinion has often been expressed that colloid glands (goiters) are due to a passive dilatation of the alveoli from the accumulation of colloid. While it is probable that in the late stages of colloid glands (goiters), obstructions and circulatory disturbances lead to passive dilatation, there is no question that the process of alveolar enlargement is always initiated as an active hyperplasia. Uncomplicated types of colloid glands (goiters) are rare in man, even in the most favorable form of goiter, namely, simple or endemic goiter in childhood. This is because of the longer duration, treatment, trauma, tumors, hemorrhage, etc. Colloid glands (goiters) may be produced experimentally in two to three weeks in animals with large actively hyperplastic thyroids by the administration of small amounts of iodin. Their spontaneous production, while tending to take place in all active hyperplasias, usually extends over months or years depending on the species of animal, age, sex, locality, treatment, nutrition, etc. The gross appearance of an uncomplicated colloid gland is almost identical with the normal thyroid except for size. The general outline follows that of the normal gland. The consistency is firm and somewhat

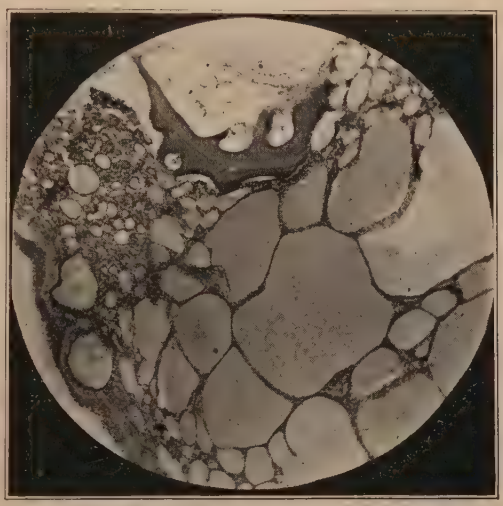


Fig. 16. Colloid goiter in bony fish (Salvelinus fontinalis), illustrating the resting or recovery stage of an active hyperplasia. Note the variations in size of alveoli, their relation to bone, flat cuboidal epithelium. (After Marine and Lenhart, J. Exper. Med., 1910: 12.)

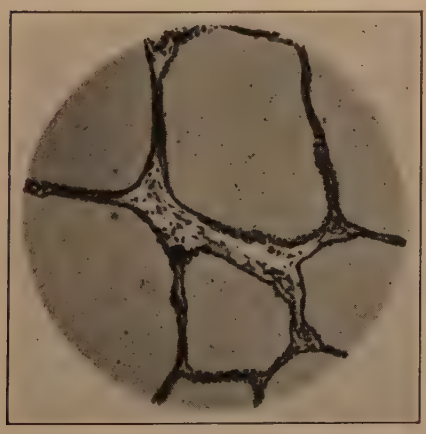


Fig. 17. Colloid goiter in sheep. (After Marine, Johns Hopkins Hosp. Bull., 1907: 18.)

elastic. The color varies from a pale translucent amber-red to a bright amber-red. The blood vessels are much enlarged, usually tortuous, and their walls are thickened. On section, the alveoli vary greatly in size as compared with the normal, which are much more uniform. The smallest are much smaller than the smallest seen in a normal, and the largest are many times larger than the largest alveoli seen in the normal gland. All the alveoli are filled with a clear amber-yellow colloid, which gives to the thyroid its characteristic translucency. Microscopically the epithelium is

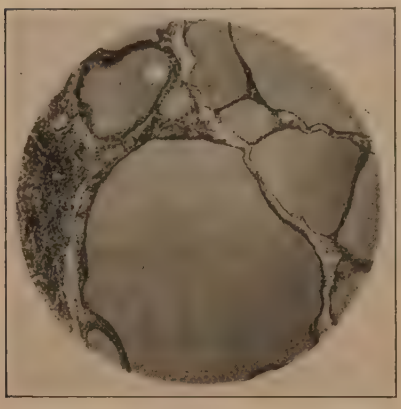


Fig. 18. Colloid goiter in man (from case of clinical exophthalmic goiter), illustrating the lymphoid hyperplasia, the irregular size of the alveoli, uniform colloid and low cuboidal epithelium. (After Marine and Lenhart, Arch. Int. Med., 1911: 7.)

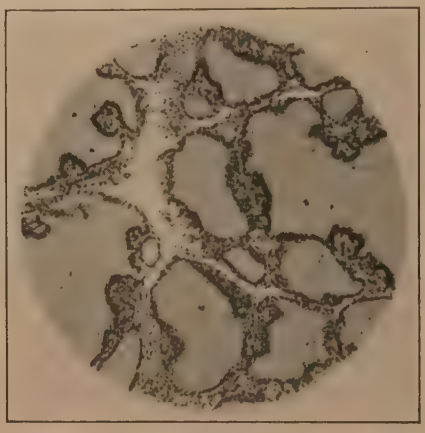


Fig. 19. Moderate active hyperplasia, thyroid of dog. (After Marine, J. Infect. Dis., 1907: 4.)

low cuboidal. The sprig-like projections (remnants of the old infoldings and plications) can be made out. These are more distinct in recent involutions than in long standing colloid glands. The stroma is increased, although there are exceptions depending on the extent of the fibrosis occurring during the stage of active hyperplasia and the extent of its absorption during the process of involution. Hyaline transformation is not infrequently seen. The arterial walls are always thickened and histologically show an obliterating endarteritis similar to that seen in the involuting thymus or uterus. The stainable colloid is of normal density and distribution in the alveoli. The percentage of iodin in the colloid gland may be as high as that of a normal thyroid, though usually it is somewhat lower. (See Figs. 16, 17, 18.)

The administration of a few milligrams of iodin daily to an animal with a hyperplastic thyroid causes a rapid involution to the colloid or resting stage. This reaction is illustrated in Figures 19, 20 and 21. Hitzig, Kocher, A., Sanderson-Danberg, Wegelin, White, Wölfler.

Summary

Summing up the previous four groups or the strictly physiological phases of goiter, it is seen that the thyroid cells have a cycle of morphological changes and, so far as we at present know, but one cycle. Beginning with the normal or colloid thyroid, this cycle is characterized by hyper-

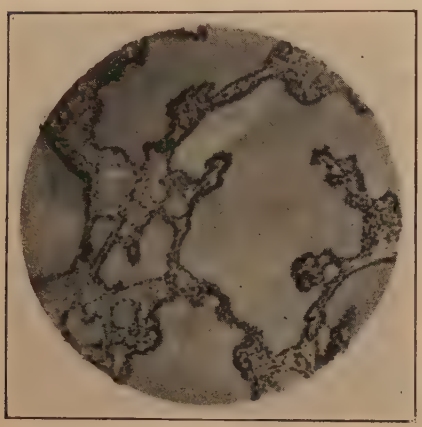


Fig. 20. Section of same thyroid shown in Fig. 19, removed 10 days later. (After Marine, J. Infect. Dis., 1907: 4.)

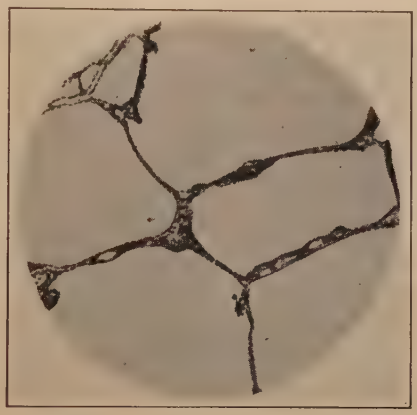


Fig. 21. Section of same thyroid shown in Figs. 19 and 20, removed 14 days later. (After Marine, J. Infect. Dis., 1907: 4.)

trophy going on to hyperplasia which terminates either in exhaustion atrophy or in involution (recovery). If involution takes place the gland returns to a functionally normal state, and anatomically to the nearest normal condition that the once hyperplastic thyroid can again assume. Anatomically, this state is spoken of as colloid gland (goiter). From this stage, the thyroid may again repeat its cycle through hypertrophy, hyperplasia and on to exhaustion atrophy or involution. Marine and Lenhart (a).

Atrophies

The thyroid is physiologically active throughout life. Its activity is most pronounced during youth and early adult life and gradually lessens with age. Several forms of simple atrophy within the limits of normal physiology may be recognized, for example, senile atrophy, atrophy following castration, the involution of hyperplasias, atrophy from disease and pressure atrophy. de Coulon, MacKenzie, Payne, Vandervelde and Henrard.

Senile Atrophy.—This is normally seen in old age and in association with many wasting diseases as in the late stage of pulmonary tuber-

culosis, marasmus, diabetes, cancer, senile dementia, etc. The gland is reduced in size, sometimes by half its original volume. This reduction in size is due mainly to losses of epithelium and colloid. The gland often is flaccid and tough, due to the relative increase in stroma. Microscopically, the blood vessels show varying degrees of sclerosis; the alveoli are smaller and more variable in size; the lining epithelium is less uniform; there is a tendency to heaping up and desquamation. Colloid material is in general much reduced, though isolated alveoli may be distended with dense colloid—true colloid retention cysts. These changes are commonly associated with other secondary changes, as scar formation, pigmentation from old hemorrhage, both in the stroma and in the alveoli, small cysts often containing cholesterol, calcification and hyaline degeneration. Pilliet.

Atrophy Following Castration and Iodin Administration.—Thyroid changes following castration or following the administration of iodin while having something in common with atrophy are more properly designated involutions. One sees from time to time descriptions in the literature describing a peculiar form of atrophy due to iodin. This is wrong. Both castration and the administration of iodin produce morphological changes characterized by flat cuboidal epithelium and dense colloid indicative of decreased cellular activity. In the case of castration this is part of the decreased demands of the organism as a whole for thyroid function. The administration of iodin lessens the cellular activity of the thyroid by supplying the distinctive element of its secretion. Vitry and Giraud.

Pressure Atrophy.—Pressure atrophy is usually seen about adenomata. The rapid growth of an adenoma stretches the surrounding thyroid tissue and if the growth is marked, pressure destruction of the alveoli of the non-adenomatous thyroid about the tumor takes place. All the non-adenomatous thyroid of a lobe may be thus destroyed. In districts where endemic goiter is common, the so-called struma nodosa, or adenomatous goiter frequently causes extensive pressure atrophy of the non-adenomatous thyroid.

Exhaustion Atrophies (see Fig. 15).—These are associated with the symptom complexes seen in Dercum's disease, in cretinism and myxedema. There is no evidence that these are primary thyroid diseases but rather the result of some systemic or general metabolic disturbance. Getsowa.

Often in young very obese individuals and practically constantly in the special form of obesity described by Dercum, one finds well marked atrophic changes. It is a widely held opinion that there is a definite relationship between the thyroid atrophy and the clinical manifestations.

The atrophies seen in endemic cretinism and in myxedema in man and the lower animals are the most striking examples of exhaustion atrophy. This subject has already been referred to under "Hyperplasias" because all the evidence indicates that these atrophies occur in the late stages of active hyperplasias and in spite of the attempts of the gland cells to re-

generate. The available evidence at present suggests that they are true work exhaustions, as can be readily demonstrated in cretinism of the lower animals where it is possible with very young cretin pups or lambs to cause the highly atypical columnar thyroid cells to return to a cuboidal form with the accumulation of colloid by the administration of small amounts of iodin or desiccated thyroid and later, by partial removal of such recovered glands, to obtain a perfectly regular and uniform active hyperplasia. Exhaustion atrophy is most commonly seen in children in endemic goiter districts and in adults in the end stage of exophthalmic goiter. The essential anatomical changes in the thyroid are similar in both cretinism and myxedema. In the typical case, the thyroid clinically is enlarged, or there is a clear history of its having been enlarged. The gland is usually very vascular. The colloid is practically absent; the epithelial cells have lost their regular and uniform type characteristic of the early stage of active hyperplasia. There is often piling up of the epithelial cells and desquamation of the partially degenerated cells. The nuclei are usually large, irregular in size, staining intensity and outline. Mitotic figures may still be observed. The alveolar spaces become smaller though still preserving the infoldings present in the well developed hyperplasia. The surrounding stroma is relatively, perhaps absolutely, increased and in animals often edematous and myxomatous. As the alveoli become smaller from the death of their secreting cells, the interlobular stroma increases and finally gives the appearance of a generalized sclerosis in which the alveolar elements appear as nests of compressed cells. In man, lymphoid foci are scattered throughout the stroma much as it is in the actively hyperplastic state of exophthalmic goiter. Most of the examples of this form of atrophy in man do not appear as simple as the above description might indicate, because they are nearly always complicated by other changes such as adenomata, cyst formation, hemorrhage, calcification,—all of which may be present in the same gland. Summing up then, the type of atrophy supervening in active hyperplasias and clinically associated with myxedema or cretinism is a cell death due to exhaustion. The process is simple but the interpretation of the anatomical changes in such glands, especially in long standing cases, may be difficult. This type of atrophy is the usual end stage of all active hyperplasias unless terminated by death or recovery of the individual, and considering the total number of active hyperplasias from all causes and in all animals, it is a rare sequel. Pasteur, Roussy and Clunet (*a*), Schultze, Sollier, West (*b*).

Degeneration

In thyroid histo-pathology, the term "degeneration" has often been misused. The commonly accepted types of degeneration as hyaline, calcareous, amyloid, parenchymatous, fatty, etc., are observed to an exag-

gerated degree because of the wide range of anatomical changes dependent upon the great variations in physiological activity. Hyaline transformation, both of the vessel walls and the stroma, accompanies normal senile atrophy. It is also seen in the stroma of long standing colloid goiters and of adenomata. The yellowish appearance on cut section of the interior of many old adenomas that have partially outgrown their blood supply is due to a hyaline change in the stroma. Microscopically in such areas the alveoli may be absent or appear as widely scattered rings of epithelial cells embedded in a hyaline matrix with few blood vessels and no recognizable basement membranes. Calcareous deposits are of frequent occurrence in human goiter. Indeed, they are almost always present in long standing simple goiters, and occur particularly in the capsule, in the stroma, the vessel walls, the scars of old hemorrhages, in cyst walls or in the hyaline and scar-like centers of old adenomas. The deposits may be very extensive and particularly in scar tissue frequently take on the structure of bone. The frequency with which one encounters bone formation in the thyroid reminds one of the frequency with which bone formation is seen in lung tissue. Amyloid infiltration is usually observed in connection with similar deposits in other organs, but may occur independently, especially in benign tumors. Parenchymatous degeneration or cloudy swelling is also seen to an exaggerated degree in the thyroid. Some writers have described it under the title of Thyroiditis Simplex. This change is best interpreted as the anatomical evidence of increased physiological activity, and is more striking than in other tissues because the thyroid is more labile. It is seen in the same associations as parenchymatous changes of other organs, that is, in acute infections and intoxications and is the precursor of true hypertrophy and hyperplasia if the cells are able to cope with the intoxication or of thyroid atrophy if it is overwhelmed by the intoxication. Fatty changes in the cell or the presence of large quantities of glycogen are particularly seen in adenomas and in non-adenomatous thyroid where the blood supply has been interfered with either by pressure, hemorrhage or edema. Eberth (*b*), Ramberg, Stoffel.

Inflammations

(Thyroiditis, Strumitis)

The infectious theory of goiter gave rise to the view that all true goiters were chronic inflammatory reactions. There is no conclusive evidence that goiter is due to an infection. The general increase in fibrous tissue and the occurrence of small foci of lymphocytes are parts of the general thyroid reaction during active hyperplasia. There is normally lymphoid tissue in the thyroid and in certain forms of thyroid hyper-

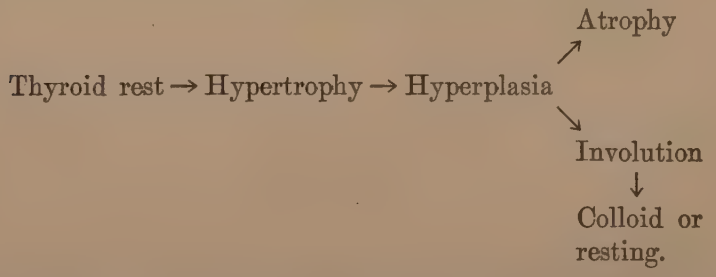
plasia, especially those associated with adrenal insufficiency, this lymphoid tissue may undergo hyperplasia as part of the general lymphoid hyperplasia throughout the body, even to the extent of forming large germinal centers. There is no basis at present for considering this inflammatory. True inflammatory reactions are rare. They are never primary. Many of the so-called forms of *acute thyroiditis* are scarcely more than active hyperemias or cloudy swellings. These conditions are not infrequently seen in acute infectious diseases, in food intoxication, drug rashes, intestinal exanthemas and following extensive skin burns. A thyroiditis due to the administration of iodin has been described. Iodin does not cause thyroiditis. The administration of large amounts of iodin to an individual with actively hyperplastic goiter may cause the gland to become very firm, even enlarged, and quite painful, due to stretching of the capsule. The thyroiditis simplex described by some authors has been referred to under cloudy swelling or parenchymatous degeneration. *Suppurative thyroiditis* may occur in the course of puerperal infections, ulcerative endocarditis, scarlet fever, typhoid fever, influenza, pneumonia, tonsillitis, and may also occur as a direct extension from adjacent structures. It is more frequently seen in thyroids that have undergone goiterous enlargement or which contain benign tumors. Thyroid tissue with impaired vitality forms excellent foci for the lodgment and growth of pyogenic organisms. Injuries, as in the old iron and iodin injections, were frequently followed by necrosis and subsequent abscess formation. In generalized tuberculosis the thyroid is commonly involved. There is no recorded instance of primary tuberculosis. Gummata are being reported with increasing frequency. Bauer, Clairmont, Davis, Dunger, Ewald, C., Hedinger, Melandri and Legg, Pollag, de Quervain, Roger and Garnier, Schutz.

Tumors

The two distinctive groups of thyroid epithelial tumors are the adenomas and carcinomas. Bircher, H., Langhars (*a*) (*b*), Marine (*a*).

Adenoma.—This group includes a very vague and indefinite series of tissue proliferations ranging from the well defined, circumscribed and encapsulated masses of glandular tissue to the diffuse, uniform hyperplasia of simple goiter. Anatomical separation of those groups which might properly be called adenomas, from those which should be grouped with simple hyperplasias, is not possible. It is possible by utilizing the biological test with iodin to make a partial separation. Such tests show that the more differentiated the tissue the more nearly it reacts with iodin like normal thyroid. Even the more undifferentiated—the so-called fetal adenomas—have some power to react with iodin and one must conclude that while anatomically and for convenience these

growths may at present be called benign tumors, they are at most only partial tumors since they have retained many of the physiological characteristics of normal thyroid. Adenomas, like fibroids of the uterus, are rarely seen except in man, and on this account, what should be the most favorable tissue for the experimental study of the general tumor problem, cannot be utilized. The nearest approach to adenoma formation in the lower animals is found in the thyroid of the white rat, but these circumscribed areas of hyperplasia are composed of well differentiated thyroid which react readily with iodin, and therefore are properly considered as part of the general physiological overgrowth. Adenomas most frequently occur in simple or endemic goiter about the age of puberty. They are also seen in congenital goiter and may develop, though rarely, late in life. They are rarely ever seen apart from goiter and therefore the sex incidence is the same as that of goiter. They may be solitary but are more frequently multiple. The view that they arise from cell rests which are present in most normal thyroids offers the best explanation of the origin of these growths. These cell rests may be considered as excess thyroid tissue beyond the needs of the organism which are slowly being destroyed, but when the stimulus for increased thyroid activity reaches the gland all the viable cells, including these cell rests, react with growth, and the type of growth morphologically depends on the degree of differentiation of the cells at the time the stimulus was applied. This hypothesis would account for the wide range of cell types from fetal adenoma to those indistinguishable from simple hyperplasia. In addition to the above range of morphological variations dependent upon the degree of differentiation of the cells at the time the adenomas start to develop, one must also recognize that these growths are capable of differentiation during their development, that is, they have a cycle of cell changes (growing, involuting and colloid or resting stage) similar to that of the normal thyroid. These may be represented in the following scheme:



The particular morphology, therefore, of any given adenoma is in part dependent on the degree of differentiation of the cells from which the tumor arose, and in part dependent on the stage in the cycle of cell changes existing at the time of examination. A simple and satisfactory anatomical classification of these growths cannot be made. In order to

provide a working basis, these growths may be divided arbitrarily and for convenience, as follows:

Simple adenoma { growing, involuting, resting

Intermediate adenoma { growing, involuting, resting

Fetal adenoma { growing, involuting, resting

Each of these groups has a growing, involuting and resting or colloid stage. Ribbert (*b*), Virchow (*a*).

Simple Adenomas.—These masses are more frequently seen in the so-called nodular goiters (struma nodosa), and make up a large pro-

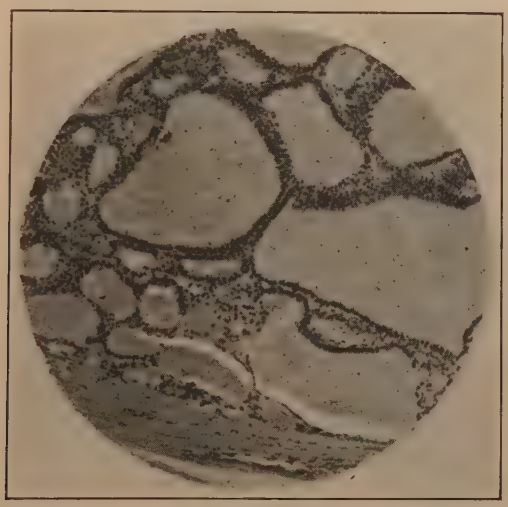


Fig. 22. Simple adenoma from endemic goiter in man, showing capsule, slight active hyperplasia of well differentiated thyroid tissues. (After Marine, J. Med. Research, 1913: 27.)

portion of the "struma knotchen" which occur commonly in the goiters of late childhood and puberty in endemic goiter districts. They are always multiple rounded masses of varying size and in their growing phases are integral parts of the general goiter, but in their late stages may become more distinct and isolated through secondary changes. The true capsule if present, is rudimentary, while in their late stages they have a well-defined false capsule derived from the stretched and atrophic non-tumor tissue. Histologically as regards epithelium, colloid, alveoli,

blood supply and stroma they conform to those prevailing in the gland as a whole. They react with iodin. (See Figs. 22, 23, 24.)

Intermediate Adenomas.—These tumors are usually multiple and on section quite distinct in appearance from the non-tumor thyroid. They share the same variations in size and number that simple adenomas do but have well formed fibrous capsules. Histologically they are composed of less differentiated and more closely packed alveoli, less stroma, less colloid and while they react with iodin it is slower and to a less degree than with simple adenomas. (See Figs. 25, 26.) Michaud, Müller, W. (*a*).

Fetal Adenomas.—These are the best known and the most distinctive

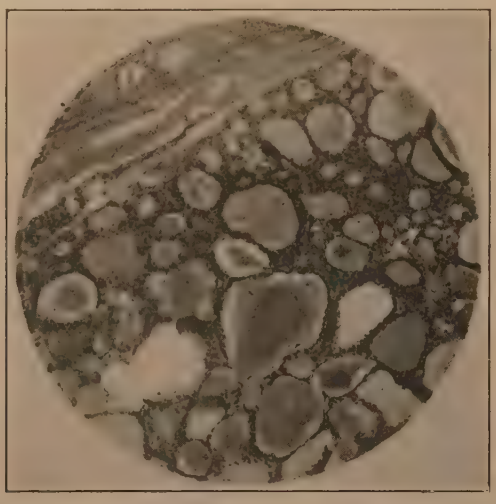


Fig. 23. Simple adenoma, colloid phase. (After Marine, J. Med. Research, 1913: 27.)

types of benign tumors. They are usually multiple and when their growth is arrested early may persist with but little change into old age. In gross appearance the smaller adenomas may be indistinguishable from large lymph foci that may be present. The larger tumors are round in form and in the developmental stage are grayish-opaque in color. The tumor issue is friable, very cellular, and there is no visible colloid. (See Figs. 27, 28, 29.) Billroth, Berard and Alamartine, Bloodgood (*b*), Delore, Goetsch (*a*).

To summarize the major features of the three arbitrary groups, it is found that all have true capsules often rudimentary in simple adenomas and progressively more prominent and distinct in the intermediate and fetal groups. The stroma is poorly developed and scanty in all, being least developed in the fetal adenomas. No trabeculæ are present, hence no lobulation as in the normal thyroid. The larger well formed vessels lie in the capsules, while those of the parenchyma have poorly developed muscular and adventitial coats. These tumors grow from the subcapsular

zone, and as their central portions become more and more removed from their blood supplies—an outgrowing of the blood supply—so to speak,

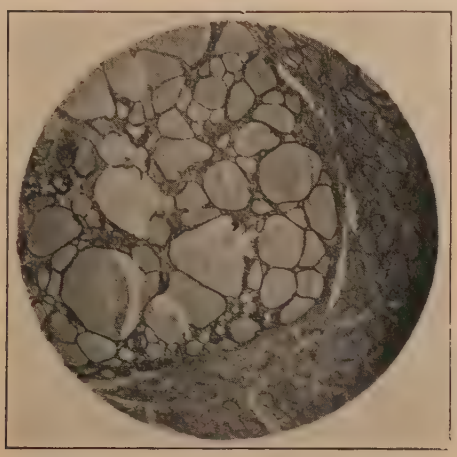


Fig. 24. Simple adenoma (colloid phase), showing the absence of true capsule but presence of a rudimentary false capsule. (After Marine, J. Med. Research, 1913: 27.)

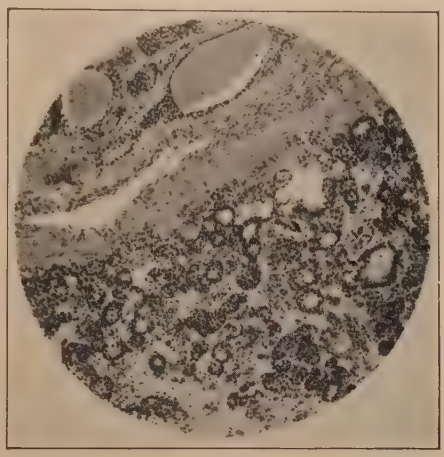


Fig. 25. Intermediate adenoma showing small but differentiated alveoli. (After Marine, J. Med. Research, 1913: 27.)

atrophy, degeneration, necrosis, cyst formation and other destructive metamorphoses occur. This tendency is most pronounced in the fetal adenomas, and less so in the simple adenomas where the blood vessels are

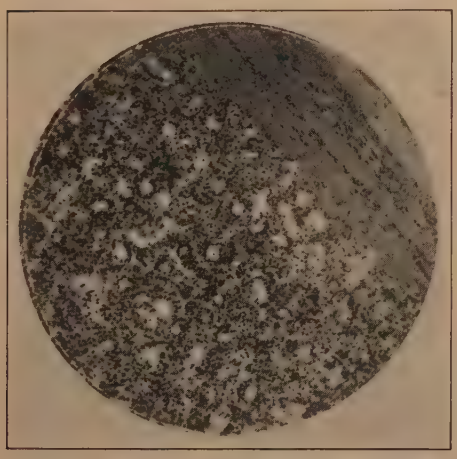


Fig. 26. Intermediate adenoma illustrating borderline type between the arbitrary divisions of fetal and intermediate adenomas. (After Marine, J. Med. Research, 1913: 27.)

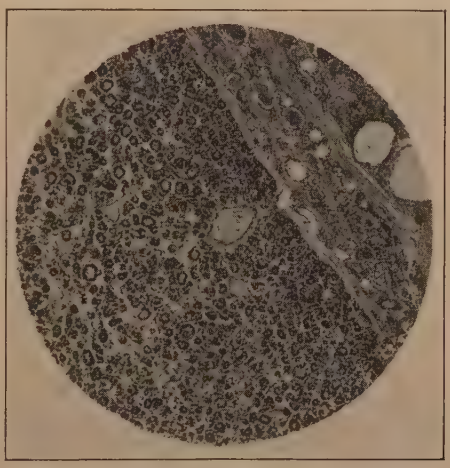


Fig. 27. Fetal adenoma. (After Marine, J. Med. Research, 1913: 27.)

well developed. The alveoli are larger and most irregular in simple adenomas, and progressively become smaller and more regular in outline

in the intermediate and fetal adenomas. The epithelium in the growing phase of simple adenomas is distinctly columnar and becomes more cuboidal in the intermediate and fetal groups. In the colloid phase all groups have cuboidal epithelium as the ruling type. Infoldings and plications are usually present in simple adenomas while they are rarely present or only rudimentary in the intermediate, and are absent from the fetal adenomas. The colloid content of all groups is much reduced during the growing phases. (The secondary and terminal metamorphoses of adenomas will be discussed under "Complications".)

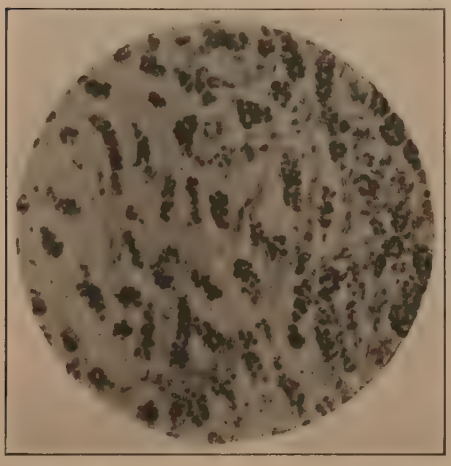


Fig. 28. Fetal adenoma, illustrating the tubular effect. Section taken from the center of an adenoma whose nutrition is impaired and illustrates the early regressive change leading to cyst formation. (J. Med. Research, 1913: 27.)

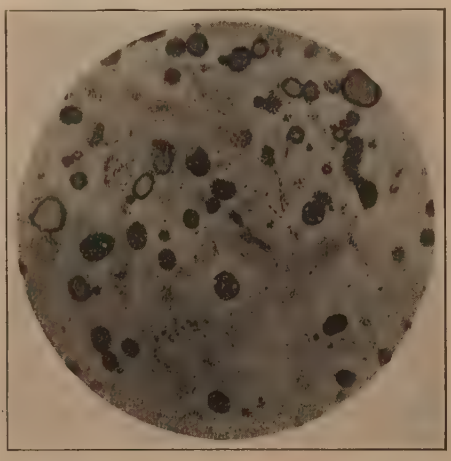


Fig. 29. Interior of fetal adenoma in colloid phase illustrating more marked degree of failing nutrition, hyalinized stroma. (After Marine, J. Med. Research, 1913: 27.)

Carcinoma.—The diagnosis of thyroid carcinoma is difficult because of the wide range of typical and atypical cell proliferation which may take place within physiological limits. The cell picture is often of little aid, and in the absence of metastases, other features such as the gross appearance, the history, and the effect of the administration of iodin should be sidered. Goiter, and particularly adenomas, are the most important precursors of human thyroid cancer. Carcinoma developing from the normal thyroid must be rare. There are reports of such cases, but all of these are susceptible of other interpretations. No satisfactory morphological grouping of thyroid cancers is possible. The more commonly observed types are:

Carcinoma simplex.
Adeno-carcinoma.
Scirrhus carcinoma.
Papillary cystic carcinoma.
Squamous cell carcinoma.

Carcinoma Simplex.—The simplex or fetal type arises from pre-existing adenomas, and it is the most frequent type of thyroid carcinoma, making up probably more than 50 per cent. These are likewise the most malignant and most rapidly growing carcinomas. They may occur at any age. The thyroid cancers seen in childhood and early adult life are usually of this type. They are encapsulated because of their origin from adenomas and may show no invasion of the capsule when lung metastases are present.

Histologically these cancers are characterized by the general absence of colloid and the tendency of the alveoli to form solid closely packed columns of cells. The cell type of this form of carcinoma is usually quite uniform. There may be some differentiation with the formation of rudimentary alveoli.

Adeno-Carcinoma.—Adeno-carcinomas include the so-called metasizing colloid goiters, and those tumors in which the alveoli become differentiated into colloid containing spaces. There may be infoldings and plications of the lining epithelium. The epithelium may be cuboidal or columnar. The cells are usually irregular with a tendency to heaping up and desquamation. These tumors may arise from the more differentiated adenomas. They form infiltrating growths. This type of carcinoma is relatively common in old dogs with long standing goiter, although adenomas are rarely observed. Cohnheim, Ewald, O., (*b*) Kocher, T. (*e*).

Scirrhus Carcinoma.—Scirrhus carcinoma is rare. Several examples have been described where the outlines of thyroid lobes slightly, or moderately enlarged, are preserved. Such glands are extremely hard. On section, the tumor resembles a diffuse, extreme fibrosis, which extends into the non-tumor thyroid without any line of demarcation. Microscopically, in the older parts there may be no glandular elements left. Nearer the periphery there are compressed, irregular strands of epithelial cells, widely scattered in the dense stroma and still nearer the growing border, normal appearing thyroid alveoli may be seen in the developing fibrosis. Marine and Johnson, Patel, v. Recklinghausen.

Papillary Cystic Carcinoma.—Tumors with papillary projections, some low and others high and arborescent, may be distinguished as a group. As a rule they grow slowly. They are not all malignant and the benign form has been designated papillary adenoma. Papillary adenomas may be present at birth. The epithelial types vary from cuboidal to high columnar. The cystic spaces may contain colloid material. Low, Zullig.

Squamous Cell Carcinoma.—Squamous cell carcinomas occasionally arise in the thyroid, and as regards structure and general appearance resemble squamous cell tumors arising elsewhere. They arise from epiblastic structures included in the thyroid, from the thyroglossal tract or from the branchial clefts. Eberth (*a*), Vevebély.

Sarcomas.—Sarcomas and mixed carcinomas and sarcomas of the thyroid are more frequently observed and more important than the old literature would indicate. They are more frequently seen in the fifth and sixth decades, and as in the case of carcinoma, are usually preceded by long standing goiter. The spindle cell and the perithelial types are the most common forms observed. The status of thyroid sarcoma is highly involved and doubtful. There is no method of distinguishing with certainty between carcinoma and sarcoma. Morphology does not offer much assistance. The frequency of occurrence of these mixed tumors (sarcoma and carcinoma) of the thyroid in many mammals; why these tumors are not more frequently seen in other body tissues, and why the etiological factors of age and preëxisting goiter are the same as in undoubted cancer —all these facts cause one to doubt the mesoblastic origin of most of these so-called sarcomas. Kaufman, Loeb (*a*), Poult, Russell and Kennedy, Saltykow, Schöne, Simmonds, Usui, Wells (*a*).

Complications

Hemorrhage.—Hemorrhages are the most frequent pathological changes in the thyroid. Small hemorrhagic areas are occasionally seen in essentially normal thyroids, but they are essentially complications of goiters. They rarely occur during the developmental stage but during its involutionary and colloid stages. Why hemorrhages should occur during the colloid phase is not difficult to understand when one recalls the fact that the developing hyperplasia is soft, compressible and elastic while in the colloid phase the gland is firmer and the alveoli distended with colloid, so that slight trauma or manipulation or even the alveolar distention is sufficient to cause the thin walled, large, sinusoid capillaries to rupture. Perhaps sudden rises in blood pressure as in violent exertions or coughing are causal factors. The thyroids of all animals are subject to hemorrhages. Anatomically, the hemorrhages may appear only as a reddish, brownish, greenish or yellowish discoloration of the colloid. Larger areas tend to encapsulation and the cavities contain brownish material, sometimes a viscid colloid mixture, while in others it is more fluid. In general, however, in the small hemorrhagic areas the colloid forms the body of the mass while the extravasated blood produces the discoloration. The term "hemorrhagic goiter" has been commonly used to describe old nodular (adenomatous), and varicolored goiters, the result of multiple small and large areas of hemorrhage of different ages. The term is not descriptive, since the hemorrhages are only secondary and complicating factors. Areas of hemorrhage frequently heal by scar. Such scars produce many of the capsular adhesions so commonly seen in old human goiters. Owing to the normal architecture of the thyroid, hemorrhage forms a starting point for most thyroid cysts. Archibald.

Cysts.—Some observers use the term "cyst" to include enlarged colloid filled alveoli and designate such goiters as "cystic goiter." This is wrong. First, because cyst formation is not a part of goiter formation, and secondly, there is no difference between the alveoli of normal glands and of colloid goiters, except size. True thyroid cysts are common for the reason that hemorrhage is common. Beck, Bloodgood (*a*), Rokitansky (*a*) (*b*).

Two essential types of thyroid cysts may be differentiated.

Cysts from hemorrhage into alveoli.

Cysts from adenomas.

Cysts due to hemorrhage into the alveoli are the usual thyroid cysts. They vary in size from a few millimeters to six to eight centimeters in diameter. The smaller ones have the slightly thickened alveolar walls as their cyst walls, while the larger cysts include in addition portions of the gland capsule or trabeculæ together with whatever new formation of connective tissue may have taken place. Calcification of the cyst wall is quite frequently observed. The cyst contents consist of blood in various stages of decomposition mixed with more or less colloid, sometimes it is brown, pasty, sometimes viscid, sometimes serous. In color the contents vary from dark-brown to clear amber-yellow. Cholesterol is frequently present in these cysts. Bradley.

Cysts arising from adenomas make up the majority of so-called surgical cysts. The primary change in the adenoma leading to cyst formation is probably an interference with the nutrition of the interior of the tumor due to outgrowing its blood supply which is entirely capsular, resulting in central necrosis. Hemorrhage then takes place and the softening may extend to the capsule. More often there is a zone of active adenoma tissue beneath the capsule varying from a few millimeters to a few centimeters in thickness. The original capsule of the adenoma forms the cyst wall. Acute, large hemorrhages may occur in cystic adenomas. Also they form excellent sites for the lodgment and development of pyogenic organisms, hence secondary abscess formation is relatively frequent. Cysts of adenoma origin make up the largest cysts seen in the thyroid. The contents of these cysts are, as a rule, more fluid than the primarily hemorrhagic cyst. The material is frequently brownish in color and may contain cholesterol and small masses or clumps of tissue débris. In long standing cysts of this origin, a clear yellow or greenish fluid is not uncommon. Clark and Farmer, Schneider, Tillaux.

Developmental Defects and Anomalies

The thyroid gland arises from a single ventral, midline "anlage" of endoderm in the floor of the primitive pharynx, grows down or is dragged down as the thyroglossal tract with the trachea and branches into right

and left lobes. Normally this tract between the foramen cecum and thyroid isthmus undergoes complete absorption very early in fetal life, leaving only the lateral lobes connected across the trachea anteriorly in the region of the third and fourth tracheal rings by a flattened band of thyroid one or two centimeters in width and less than half these measurements in thickness. The human thyroid especially, although other mammals as well, exhibits a wide range of abnormalities which in one way or another center about the development, downgrowth and fate of the thyroglossal tract. The most common of these abnormalities is the presence of a pyramidal process. This is most frequently seen in association with endemic goiter and indicates an increased functional need for thyroid tissue at the time when the tract should undergo absorption. The pyramidal process usually replaces the isthmial band of which it is the unabsorbed portion. There may be two pyramidal processes due to the tract dividing high up. In that event there is a pyramidal process extending obliquely downward and outward to each lateral lobe and an absence of the isthmus. The pyramidal process may connect directly with the right or left lobes, more frequently with the left. Occasionally there is complete absorption of the isthmus as in many lower animals, e.g., dog, sheep, etc., leaving the two lobes isolated. Rarely one of the lobes (more frequently the right) is rudimentary or absent. This is due to the failure of the thyroid anlage to divide. Similar anomalies are seen in the lung. Of greater importance are those cases where the descent of the thyroid "anlage" is arrested above the hyoid bone. In such instances there is usually a large thyroid mass beneath the foramen cecum and no thyroid tissue below the hyoid. Such cases unfortunately have been operated upon for the removal of so-called sublingual goiters. There may, however, be thyroid tissue around the foramen cecum and in interrupted masses or in a continuous column from the foramen through the hyoid bone and terminating in the pyramidal process co-existent with well formed lateral thyroid lobes. This condition again is more frequently seen in association with endemic goiter. These more or less isolated masses of thyroid tissue along the line of descent of the thyroglossal tract have been designated as "lingual," "sublingual," "suprahyoid" and "infrahyoid" thyroids. Born, Chamisso de Boucourt, Mayo, C. H. (*b*), Streckeisen.

Complete absence of the thyroid anlage occurs. All these variations in the development, descent, bifurcation of the tract and the failure of the thyroglossal tract to undergo normal absorption have been of great aid in the development both of our knowledge of the embryology of the thyroid and of the structures—parathyroids, thymus and postbranchial bodies—derived from the branchial clefts. Thyroglossal cysts are formed from the thyroglossal duct by partial atresia or by an arrest of its physiological absorption. Two types are seen: (1) those lined with

squamous cell epithelium and (2) those lined with ciliated epithelium. As the upper part of the thyroglossal duct usually has squamous epithelium, and the lower part ciliated, the type of cyst indicates roughly its origin. In many of the cases with thyroglossal cysts or with persistence of the thyroglossal tract, the hyoid bone contains a foramen through which the tract passes. This is due to the hyoid developing much later in embryonic life than the thyroid, and when the tract persists the hyoid is developed around it. Accessory or aberrant thyroid tissue, apart from that described above in relation to the thyroglossal tract, is most frequently seen in the region of the ascending and transverse portions of the aortic arch. Occasionally, thyroid fragments are present in the thymus, at the bifurcation of the trachea and as far down as the esophageal opening in the diaphragm. In the large teratomatous growths of the branchial cleft and ovarian regions thyroid tissue is frequently present. Many instances of the occurrence of thyroid tissue in ovarian tumors and cysts have been reported. The cystic spaces of such tumors and cysts, filled with desiccated albuminous material, often resemble thyroid alveoli and are only differentiated from thyroid by a test for iodin. Bauer, E., Erdheim, S., Erdheim, J. (*b*), Kanthack, Kadyi, Madelung, Marshall (*a*) (*b*), Schwartz and Thompson, Ungermann, Schilder.

Clinical Syndromes Due to Thyroid Diseases . . . . . .

. . . . . *C. P. Howard*

Dysthyroidism—Hyperthyroidism—Synonomy—Definition—Incidence—Etiological and Predisposing Factors—Pathogenesis—Symptomatology—The Goiter—Disturbances of the Autonomic System—Cardiovascular Symptoms—Cutaneous Symptoms—Gastro-Intestinal Symptoms—Respiratory Symptoms—Urogenital Symptoms—Menstrual Disturbances—Relation to Pregnancy—The Breasts—Libido and Potentia—Urinary Constituents—Disturbances of Metabolism—Associated Endocrinopathies—Neuromuscular Symptoms—Symptoms in the Hematopoietic System—Complications—Clinical Types of Exophthalmic Goiter—Diagnosis of Exophthalmic Goiter—Course and Duration—Prognosis—Treatment.

Clinical Syndromes Due to Thyroid Diseases

Dysthyroidism

C. P. HOWARD

IOWA CITY

This term has only recently made its appearance in the medical literature, and has been employed rather loosely to indicate quite distinct groups of cases. It has been used either as a synonym for hyperthyroidism or to indicate a particular group of cases with symptoms supposedly due to both a diminished and an increased activity of the thyroid gland.

Swan (*a*) was apparently the first to use the term—in 1916—as a synonym of exophthalmic goiter but offers no explanation for so doing. While this writer was one of the few, if not the only one, to employ the word in the title of his paper there have been several writers who in the course of their articles have expressed the opinion that the symptom complex of Graves' disease may not after all be due to hyperthyroidism or increased normal secretion but rather to a perverted secretion, that is to say, to dysthyroidism.

The most important justification for the hyperthyroid theory of Graves' disease is that the nitrogen runs high in both Graves' disease and the intoxication produced by large doses of thyroid extract, while hypothyroidism, whether experimental or clinical, is characterized by a reduced nitrogen metabolism.

Following the example of Cushing, who speaks of dyspituitarism rather than hyperpituitarism to describe a symptom complex due to disturbed hypophyseal function, we might do well to drop the term hyperthyroidism once for all and speak only of dysthyroidism.

There is a certain analogy between the disturbances of both the thyroid and pituitary glands; thus in both a diminished function can be readily recognized and what is still more important can be reproduced in man and in the experimental animal by the surgical removal of one or other gland. Thus removal of the thyroid gland in man results in hypothyroidism, with the resulting well known syndrome of myxedema. A similar picture can be produced in the sheep and dog. So, too, a destructive lesion of the hypophysis leads clinically to adiposity with skeletal and sexual infantilism when it appears in childhood (Fröhlich syndrome) and to

adiposity and sexual infantilism of the reversive type when it originates in the adult. Cushing, by his brilliant experiments on dogs, has been able to reproduce a similar picture.

Further, feeding the human or laboratory animal suffering from operative or acquired forms of hypothyroidism with either the whole thyroid gland or the thyroid extract or its active principle thyroxin, will cause all the symptoms to disappear and the subject to return to normal. Somewhat similar, if less striking, results can be obtained when one feeds the hypopituitary patient or animal with full doses of the extract of the whole pituitary gland.

In marked contrast to the almost complete case that has been established for the hypofunction of both thyroid and pituitary, is the state of our knowledge of hyperfunction of these two glands. Cushing himself, as well as other workers in experimental physiology have failed to reproduce hyperpituitarism in the laboratory animal. Further, clinical hyperpituitarism as represented by gigantism or acromegaly (according as to whether the syndrome began in childhood or adolescence) sooner or later develops symptoms of hypofunction, so that Cushing prefers to speak of the condition as dyspituitarism and not hyperpituitarism. Might it not be safer, until our knowledge of the physiology and pathology of the thyroid gland is more accurate, to speak of the clinical syndrome of exophthalmic goiter, whether larval or complete, as one of dysthyroidism? This idea is not original with me, but has been suggested by personal conversations with Cushing and the reading of much of the voluminous endocrin literature.

The usual meaning that is intended for dysthyroidism is, however, not to indicate a confession of ignorance like that given above, but rather to call attention to certain larval and atypical forms of exophthalmic goiter which present evidences of an alternative hypo- and hyperthyroidism or a peculiar combination of the two at the same time. This is the sense of the term in the articles by Bram (*b*) and Bertine. The latter noted in a series of one hundred and thirty-four patients suffering from various types of thyroid disease thirty-three who combined the elements of a partial Graves' disease with a suggestion of myxedema in a way that no mere variation in the quantity of the thyroid active principle will account for; for instance, nervousness, tremor, more or less emaciation and irritability of the pulse may be associated with lassitude, inertia, emotional depression and headaches; or again there may be on the one hand tachycardia and sweating and on the other obesity, constipation and asthenia. We have all seen such cases each year and most of us have considered them as originally cases of mild hyperthyroidism due to hyperplasia of the gland which gradually gives way to a more evident hypothyroidism as the degeneration of the gland tissue progresses and the active principle is secreted in insufficient quantity. This explanation still seems logical for

the case of Graves' disease which years later presents a typical picture of myxedema. It, however, cannot suffice for the coexistence for months or years of a group of symptoms which are explained on the basis of hyperthyroidism and another group of symptoms attributed to hypothyroidism.

Klose has no doubt that exophthalmic goiter and the hypothetical hyperthyroidism are qualitatively different; he believes that Basedow's disease and iodin poisoning are probably the same, but does not think that the "Iod-Basedow" complex of Kocher is identical with iodin-thyroidismus as has been suggested by Revilliod, Jaunin and Kocher. Klose from his own experiments accepts as a working hypothesis that exophthalmic goiter is a chronic poisoning from a false or masked iodin compound which is more closely related to the inorganic iodin than to the thyreoglobulin. To this theoretical substance he has given the name of Basedow-iodin to distinguish it from the thyreoglobulin of the normal gland.

Further, Plummer (*a*) has noted the presence of a considerable group of toxic non-hyperplastic goiters presenting a variable histopathology sometimes degenerative in type. Many of these cases have been wrongly diagnosed by the clinician as exophthalmic goiter. The principal characteristics of this group according to both Plummer and his surgical associates Judd and Balfour are briefly as follows:

(1) Its chronicity; an average developmental period of over fourteen years as compared with one averaging nine months in the hyperplastic toxic goiter of Graves' disease.

(2) The relative absence of acute toxic symptoms, diarrhea, tachycardia, etc.

(3) The absence of exophthalmos.

(4) The slow development of chronic cardiovascular changes.

This is really the toxin-generating adenomatous thyroid producing what Kocher calls the goiter heart. Although differing from exophthalmic goiter it is quite possible in the opinion of Judd that the same symptoms are produced by the same agent or toxin. The thyroid glands of the thyrotoxic type vary considerably; a patient who has only a small adenoma of the thyroid may have a very marked toxemia; other thyrotoxic patients may have a general diffuse colloid enlargement with small adenomata distributed throughout the gland. The enlargement is of the colloid adenomatous type; in some instances the colloid predominates, in others the adenomata. The degree of intoxication seems to coincide with the amount of degeneration in the adenomata and the surrounding thyroid tissue. Exophthalmos is never seen accompanying the purely thyrotoxic gland. The thyrotoxic patient has no definite tremor, though there is often nervousness during exhaustion. The pulse is that of a dilated and damaged heart and usually there is a marked increase in blood pressure. There is a theory that in thyrotoxic goiter the symptoms are produced by the absorp-

tion of the products of degeneration in the adenomata or in the thyroid itself. Ligation of the vessels does not result in the marked improvement that occurs in exophthalmic goiter from this procedure. However, in Judd's opinion iodin seems to increase the symptoms of the thyrotoxic patient. We believe that this group of thyrotoxicoses could also be covered by the term dysthyroidism to distinguish it from the characteristic picture of Graves' disease.

As has been succinctly expressed in a recent editorial by Hoskins, "The trend of literature of recent years is towards a conclusion that Graves' disease is essentially a hyperthyroidism." Most writers use the terms interchangeably. As has been said the most important justification of the practice is the high protein metabolism in both the clinical syndrome and the experimental hyperthyroidism in contrast to the greatly reduced nitrogen metabolism of both the clinical and the experimental hypothyroidism. Hoskins believes that the simplest explanation of these facts is that the thyroid furnishes a hormone which serves as a general cell stimulant; in the event of a diminution of this stimulant the cell functions at a reduced rate. But why should an organism or a cell be intrinsically adjusted to a low level and be dependent upon a stimulant to keep it up to normal? The true explanation is not probably so simple.

The crucial test as to whether or not Graves' disease is the result of pure hyperthyroidism would be to reproduce the symptomatology of hyperthyroidism by the administration of thyroid gland or its extract. Crotti concludes that this has been satisfactorily done, though the majority of the students of this subject are not yet convinced.

The coexistence of Graves' disease simultaneously with hypothyroidism which has been reported as occurring not infrequently by many authors, renders untenable the theory that Graves' disease is a simple hyperthyroidism. Thyroid secretion cannot be both increased and decreased at the same time. No explanation of this paradox as yet submitted suffices to controvert this fact.

Furthermore, cases in which thyroid medication has proved of benefit in Graves' disease have been reported from time to time. Such in substance is the presentation by Hoskins of this dilemma.

Janney (*b*) offers an alternate theory—a dysfunction of the thyroid gland as the cause of Graves' disease. He believes, therefore, that there is a toxic element in Graves' disease, the toxin being derived possibly from the thyroid hormone which might be readily split into intermediate decomposition products, one or more of which may be toxic. Ordinarily this hypothetical toxic substance would be further acted on in the thyroid gland itself and be discharged thence only in some harmless or even beneficial form. But, writes Janney, "it is possible that various factors might disturb the normal synthesis of the hormone, the result being the premature discharge of the toxic intermediary product into the circula-

tion." "The factors producing this condition might be the well known causes of exophthalmic goiter." "The result of the premature discharge of the hypothetical toxic intermediary product would be an impoverishment of the gland of the thyroid hormone, which would explain the fact that Graves' disease goiters are poor in iodin and especially in the active alpha-iodin proteins." "Kendall (*g*) and Wilson report that the typical goiter of Graves' disease contains but one-fiftieth to one-twentieth of the total active iodin present in the normal thyroid gland; if the hyperthyroid theory were correct, more iodin, not less, should be present in such hyperfunctioning glands." "The decreased production of the normal hormone due to the causes mentioned would be accompanied or followed by signs of thyroid insufficiency." On these grounds Janney accounts for the occurrence in Graves' disease of such symptoms as goiter, the various cutaneous changes (as atrophy, pigmentation, scleroderma, brittleness and loss of hair, the rare abnormal deposits of fat), imperfect ossification and epiphyseal union, fatty degeneration of the heart and skeletal muscles, the mononucleosis, the metabolic disturbances of delayed glucose assimilation, creatinuria and growth disturbances in the youthful case. Certain symptoms as weakness, loss of weight and creatinuria may properly be assigned to either the presence in the blood of the hypothetical toxin or to a deficiency of the normal hormone. The evidence as to whether there is actually a toxic substance present in the blood stream in Graves' disease is very meager and as yet unconvincing. Janney's paper should at least stimulate further research along these lines. It is of interest, if not of actual significance that Caro as well as Klose have demonstrated the toxicity of the urine in exophthalmic goiter, while recently Blackford and Sandford found a depressor substance in the thyroid gland and in the serum of patients with Graves' disease.

Hyperthyroidism

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INTRODUCTION

Synonomy.—This is a term of comparatively recent date used to indicate a hyperfunction of the thyroid gland. Until quite recently the fully developed state of hyperthyroidism was considered to be illustrated by the symptom-complex, commonly called exophthalmic goiter, just as the fully developed stage of hypothyroidism was exemplified by the disease myxedema.

Whether this is the absolutely correct view or whether Graves' disease is more rightly to be regarded as dysthyroidism, will not be discussed at

this juncture. We will content ourselves with following the usual custom of including under the term of "Hyperthyroidism," both the fully developed picture of "exophthalmic goiter," and the "larval forms" or "les formes frustes" of the French. The only distinction to be made between simple hyperthyroidism and exophthalmic goiter is that in the former both the exophthalmos and the goiter may be absent at the time of observation; subsequently the goiter and exophthalmos may develop but this is neither invariable nor inevitable.

The following designations of the malady under discussion are to be found in the literature:

Exophthalmic Goiter.—Parry's disease, Graves' disease, exophthalmic bronchocele (Laycock), cardiothyroid exophthalmos (Walshe), exophthalmos anemicus (Mackenzie), anemic protrusion of the eyeballs (Taylor) in Great Britain; Basedow's disease, hyperplastic toxic goiter (Plummer) in America; Glotz-augenkachexie (Basedow), Glotzaugenkrankheit, die Basedowsche Krankheit, Struma exophthalmica in Germany; Maladie de Graves (Trousseau), cachexie exophthalmique, dyscrasie exophthalmique, exophthalmie cachectique, tachycardia strumosa (Lebert) in France; Morbo di Flajani, struma seu gozzo esoftalmico in Italy; bocio exoftalmico in Spain; Thyrotoxicosis (Kocher) in Switzerland.

Of these twenty-one synonyms for the clinical syndrome of exophthalmic goiter, those in most common use are Graves' and Basedow's disease. To whom belongs the right of priority has no doubt been made clear by the writer of the section on the history of diseases of the thyroid gland.

Definition.—Exophthalmic goiter is tersely defined by Osler in his well known text-book, as "a disease characterized by goiter, exophthalmos, tachycardia and tremor, associated with a perverted or hyperactive state of the thyroid gland." After looking over a score or more definitions of the disease we decided that this was possibly the safest one to adopt. We however believe we can accept Plummer's (*b*) proviso, namely that the term exophthalmic goiter should be reserved for cases running a certain definite course, associated with parenchymatous hyperplasia of the thyroid gland. This would include all cases with the cardinal symptoms of exophthalmos, tachycardia and tremor together with macroscopical or microscopical hyperplasia of the thyroid without necessary evidence of an actual struma.

Incidence.—An exact idea of the true incidence of the disease is difficult to obtain. Many cases were overlooked in the various clinics of the metropolitan hospitals of Europe and America in the latter half of the nineteenth century and now statistical studies have been largely abandoned. However Samuel West (*a*) in 1886 noted three cases among 3,179 out-patients at the Chest Hospital, Victoria Park, London,—an incidence of about 1 in 1,000. George Dock (*b*), formerly of Ann Arbor,

Michigan, reports 52 typical cases among 5,000 admissions to the Medical Clinic of the University of Michigan—or about 1 in 100—a very much higher incidence than that of West. Paessler, of Jena, which is in a goitrous district of Germany, noted 58 cases among 2,800 patients, or an incidence of about 1 in 50. In our own medical clinic in Iowa City, which corresponds very closely to that of Dock both in its geographical position and its consulting character (by which I mean both draw material from a large rural community of about two millions of people) there were eighty-eight cases among 7,907 medical admissions, or, in other words, an incidence of 1 in 90.

Etiological and Predisposing Factors.—*Climate, Race and Country.*—It seems to be as prevalent in one country as another. The question has naturally arisen: Does the distribution of Graves' disease run parallel to that of goiter? According to George Murray (*b*) it is not more frequent in the so-called goitrous districts of England, viz., Kent, Surrey, Wiltshire and the Thames Valley. Dock (*a*), on the other hand, noted that in Michigan, not only was simple goiter very common, occurring as it did in 10 per cent of all young women, but exophthalmic goiter itself was very common (32 cases among 4,000 admissions). Moffitt of California has noted that it is more common on the shores of San Francisco Bay than in the other counties of the state, but gives no comparative figures regarding simple goiter. Albert Kocher (*b*) writes of his experience in Switzerland as follows: "It is just as frequent in goiter regions as elsewhere, with the difference, however, that many cases in the goiter-regions run a milder course, partly because they come under observation earlier on account of the presence of ordinary goiter, and partly because goiter formation, inasmuch as it reduces the quantity of functionating tissue and impairs the vascularity, is antagonistic to thyrotoxicosis."

Sex.—Women are much more frequently affected than men: the ratio is variously stated as 13, 8, 5 or 2 to 1 by the different authorities. The higher incidence in the female is true in childhood as well as in later life—a contrast to cretinism which affects nearly as many males as females. To account for the variation between the figures of 13 to 1 and 2 to 1, Mackenzie (*c*) admits of a possible variation in the proportion of the disease in the two sexes in different countries: thus according to Charcot the disease in France was only a little less frequent in the male, and Eulenburg in Germany found the proportion of female to male as two to one: in England, on the other hand, the proportion was much higher as illustrated by Mackenzie's own series in which there were only 45 males in a series of 438 cases, and that of George Murray (*e*), whose series of 180 cases included only 10 males. Further it would seem that relatively more male cases are seen in private practice than in hospital: Thus Buschan, in a series of 980 cases collected from various sources, found 805 females and 175 males—a proportion of nine to two. Mackenzie also offers as a

further explanation of this discrepancy, that on account of their comparative rarity, male cases are more frequently reported than the female. None of these objections can be offered to the figures from the Mayo clinic, which show that among 2,928 cases of exophthalmic goiter, 85 per cent were women and 15 per cent were men—a ratio among hospital cases of about 5.6 to 1—a proportion which should stand for the United States, at least, as approximately correct.

Age.—Most are agreed that the age of greatest susceptibility lies between the sixteenth and fortieth years—that is to say, between puberty and the menopause. Cases in childhood have been reported, even as early as two and a half years. Lewis reported in a series of 1,512 cases from the Mayo clinic, five cases under ten years of age, all of the patients being girls. In Buschan's series of 495 cases, 15 were under ten years and 31 over fifty years of age. Charcot (*b*) saw a case at sixty years. At all events it is very rare after the fiftieth year, and when reported it has usually been in the male sex, though Barker (*b*) speaks of having seen it in a woman over sixty.

Heredity.—A predisposition seems to exist in certain families, and one can speak of a thyroid diathesis. Buschan reports a large series of cases with this familial tendency. Mackenzie (*c*), too, elicited a history of familial predisposition in 44 of his series of 438 cases. Oesterreicher reports a remarkable family; the mother, who was hysterical, had ten children, eight of whom were the subject of exophthalmic goiter, and one of these had three children with the same disease. In Rosenberg's series there were a grandmother, father, two aunts, and two sisters affected. Moss also reports a patient with Graves' disease whose mother and sister were similarly affected. Thus the disease sometimes affects several members of the same family or it may occur in successive generations. But what even better still illustrates the "thyroid diathesis" is the occasional incidence of exophthalmic goiter and myxedema in the same family: thus Arthur Maude reports the case of a myxedematous woman with a son and a daughter affected with Graves' disease, and Oppenheimer the cases of two sisters, one with myxedema and the other with Graves'.

Obesity and the various neuroses are thought by the French clinicians to be more frequent in the families of patients with exophthalmic goiter than is normal.

Swan (*a*) was struck with the frequency in the history of his fifty cases of exophthalmic goiter, of heart disease, nephritis, tuberculosis and carcinoma; he suggests that the children of such parents are started in life with a constitution below par and with the passing of the years various disturbances are followed by the development of exophthalmic goiter.

Habits and Occupation.—The excessive use of tea, coffee, tobacco or alcohol plays no rôle in the predisposition to the disease, according to Swan and others who have studied this question. While occupation is no

apparent factor in the female, it is probably significant that a considerable number of males have been engine-drivers, station-masters, stock brokers and persons in other occupations involving mental strain.

Fright and Mental Anxiety.—While fright has always been much emphasized as an exciting cause, careful cross-examination of the patient will usually reveal the fact that the disease preëxisted in a mild or latent form before the mental shock. Nevertheless all writers are in the habit of pointing out the close resemblance between fear and exophthalmic goiter: thus Mackenzie (*b*) aptly puts it: "The descriptions given by Darwin and Sir Charles Bell of the condition presented by persons under the influence of intense fear at once suggest the symptoms of exophthalmic goiter." "The heart beats rapidly and forcibly, the eyes become prominent, the thyroid is swollen, the limbs tremble, the skin becomes red or very pale and sweating, vomiting and diarrhea may appear." Among the causes assigned by the patient for the onset of the disease are a fall from a height or into the water, an injury to the head, receipt of bad news or being attacked by thieves.

Closely related to sudden fright is prolonged mental anxiety or worry especially if associated with physical exertion and loss of sleep. This is notoriously true of war: thus Gowers says in his text-book that many cases of exophthalmic goiter occurred in Alsace and Lorraine during the Franco-German War of 1870. Many cases of so-called "neurocirculatory asthenia" of soldiers have been assigned by Harlow Brooks to hyperthyroidism brought on by the two factors of mental anxiety and physical exertion. Buschan probably over-emphasized the neuropathic origin of the disease, though Mackenzie (*c*) elicited a previous history of mental shock, strain or worry in one-third of his 438 cases. While it must be admitted that a large proportion of the patients with exophthalmic goiter give a previous history of nervousness or even of nervous prostration, we must agree with Dock (*b*) when he states that "the neurotic subjects and families are much more likely to have gastric or sexual neuroses than exophthalmic goiter."

Infections.—*General Infections.*—Coryza, sinusitis, tonsillitis and other acute infections, as influenza, often precede the symptoms of exophthalmic goiter. Such was the case in 25 per cent of W. G. Thompson's series of 80 cases. In Swan's (*a*) series of fifty the disease appeared after an acute infection in 13: the latter included typhoid, scarlet fever, influenza, tonsillitis, diphtheria, etc. Other authors have suggested rheumatic fever, measles, mumps, pertussis and malaria as of possible etiological importance. In a small number of cases acute thyroiditis is suggested by a swelling of the thyroid gland during or after the acute infection, as was noted by Reinhold in a case of influenza. Again, in patients with simple parenchymatous goiter, an acute infection of any region may change the clinical picture to one of hyperthyroidism. It is interesting to note that

Halsted has suggested infection as a probable explanation for the thyroid hyperplasia noted by him following partial thyroidectomy in dogs; when his assistant used most rigorous aseptic procedures not a single animal showed the usual post-operative hyperplasia.

Tumors of the thyroid may be followed by signs of hyperthyroidism, though not usually.

Syphilis, especially in the secondary stage, is a frequent cause of a strumitis, according to Engel-Reimers, and is occasionally associated with symptoms of hyperthyroidism, viz., tremor, tachycardia and insufficiency of convergence. Schulmann has also reported some cases of hyperthyroidism due to a thyroiditis of both the secondary and tertiary stages of syphilis: he considers the secondary cases amenable to antiluetic measures (but not the tertiary). Clark's case of exophthalmic goiter was believed to be due to congenital syphilis. It was that of a young woman with skeletal signs of hereditary syphilis and a strongly positive Wassermann reaction, who developed very acute symptoms of exophthalmic goiter, which responded promptly to antiluetic medication. In Swan's series of fifty cases of exophthalmic goiter there was a history of lues, and that questionable in only one case. Yet Castex in 1919 wrote: "The most frequent cause among us (i. e., Argentinians) of disturbances of thyroid function is syphilitic infection either acquired or inherited." In spite of the above abstracts from the literature, we must confess that proof is still lacking that syphilis plays any but a minor rôle in the etiology of exophthalmic goiter.

Tuberculosis.—The frequency of hyperthyroidism in tuberculous patients was first noted by Stanton, Dumas and Hufnagel. Levy found 13 cases of Graves' disease among 170 tuberculous patients. Mackenzie (*b*) believes that such an experience must be quite exceptional, as he has seen only one mild case of Graves' disease in a tuberculous patient.

Pregnancy and Lactation.—These factors play an important but by no means a consistent rôle. Thus sometimes the symptoms of exophthalmic goiter begin during pregnancy or the puerperium, while on the other hand many patients with Graves' disease improve during pregnancy and do not afterwards relapse, according to the observations of Charcot (*b*) and, more recently, of Dock (*b*). It has not been definitely shown that disease of the gonads, or orchitis, and oöphoritis have a definite bearing upon the etiology of hyperthyroidism, though Hoennicke, who noted the relationship between osteomalacia and Graves' disease, suggested an ovarian source because of a supposed connection between osteomalacia and ovarian disease; however true this may be it is, needless to say, an exceedingly rare coincidence.

Nasal disease has been emphasized by many, some even suggesting that swelling of the nasal mucosa can reflexly produce the syndrome and that cauterization of the nose will cure the disease!

Iodin and Thyroid Extract.—The prolonged use of iodin as well as of thyroid extract has called forth the symptoms of hyperthyroidism in some cases. Theodore Kocher (*h*), in a long article entitled "Iodbasedow," states that Rilliet in 1860 first described exophthalmic goiter under the name of "Iodisme constitutionel." Kocher reports the case of a young woman with a small goiter of years' duration, who developed symptoms of hyperthyroidism following the use of iodin ointment. He believes it is a common cause of the disease. There are many reports in the literature of cases of acute thyroid poisoning following the prolonged or excessive use of thyroid tablets for obesity or some other malady. These cases have shown palpitation, tachycardia, tremor, nervousness, sweating and a gastro-intestinal irritation, but never the exophthalmos or goiter.

Pathogenesis.—Pierre Marie (*a*) has rightly said apropos of exophthalmic goiter: "There are in pathogenesis as in therapy many theories but little truth."

Four theories have been advanced to explain the method of production of the disease. The first two—the toxic and the infectious—will receive but scant consideration.

The Toxic Theory presupposes a chemical alteration of the water supply, as has been advanced by Marine and others before him for epidemic goiter. We have already pointed out the divergence of opinion as to the relative geographical distribution of the epidemic or endemic form of goiter and exophthalmic goiter.

The Infectious Theory emphasizes an infection of the water supply by Bacillus coli communis or even an auto-infection of the patient by the normal or abnormal bacterial flora of the intestinal tract. McCarrison (*e*) has made out a rather good case for this method of production of epidemic goiter, but makes no direct suggestion as to its applicability to exophthalmic goiter. Neither theory is universally accepted, as the observations forming the basis of both theories up to the present time lack confirmation. In any event, as Williams asks, does the provocative agent act through the medium of the sympathetic system or directly by a chemical action on the thyroid gland?

The two main theories are the thyrogenic and the neurogenic, each of which will be discussed at length.

Thyrogenic Theory.—This theory, though first outlined by Rehn in 1883, was elaborated by Moebius in 1886 into its present form. It was soon accepted by Stewart and Gibson, Murray, and Mackenzie in Great Britain, and by Mueller (*a*) and Kocher on the Continent.

It supposes an intoxication from a morbid or excessive production of the thyroid secretion, or, in Moebius' (*b*) own words, "Graves' disease is an intoxication of the body by a morbid activity of the thyroid gland." It has substantial support in many of the well established clinical and experimental facts, among which are the following:

(1) The contrast presented by exophthalmic goiter (hyperthyroidism) and myxedema (hypothyroidism). (2) The results of grafting or of feeding with thyroid gland or, better still, by the exhibition of thyroid preparations. (3) The result of thyroidectomy in relieving the symptoms of Graves' disease. (4) The occasional recovery from exophthalmic goiter and the sequence of myxedema. (5) The microscopic evidence of pathological changes in the gland. (6) The coincidence of the first clinical symptoms with the swelling of the gland.

This theory is strongly supported by Murray (*b*) who, however, admits that "it is quite possible and indeed probable that the secretion is not only increased in quantity but also altered in character." Dysthyroidism or intoxication by an altered secretion had been previously suggested by Oswald and Minnich. This, Murray admits, can only be proven when more is known of the normal secretion of the thyroid and its physiological action.

However, to return to the hyperthyroid theory proper, if we consider that the exhibition of thyroid extract never produces all the symptoms in fact, not even the cardinal ones of Graves' disease, and that the anatomical changes in the thyroid of Graves' disease render hyperplasia of the tissues probable only after the onset of the disease, and are followed later by a qualitatively altered activity of the gland, the assumption of a simple quantitative hyperfunction of the thyroid gland as the cause of the symptom-complex of Graves' disease cannot be upheld. Therefore, von Leube thinks of a toxin which is developed by a qualitative activity of the gland and which, introduced into the blood stream from the thyroid, would cause an intoxication, especially of the nervous system. However, so long as we have no positive knowledge regarding the physiological significance of the activity of the thyroid gland and are not able experimentally to obtain any insight into the action of the toxin of Graves' disease, nothing remains for the present but to abandon a positive opinion regarding the pathogenesis of exophthalmic goiter.

Janney (*b*) believes that a survey of the evidence that exophthalmic goiter is due to *hyperfunction* of the thyroid gland renders the acceptance of this view very difficult. He advances the following objections: (1) There is no apparent need for the increased activity as is usually the case when an increase in functional activity occurs. (2) There were present a considerable number of toxic non-hyperplastic cases in the large series reported by Wilson and Plummer from the Mayo Clinic. (3) Even the typical exophthalmic goiter contains but one-fiftieth to one-twentieth of the total active x-iodin present in normal thyroids, according to Kendall and Wilson. (4) Exophthalmic goiter is not infrequently found in families having hyperthyroid members and the combination of the two has been frequently observed in the same person. (5) Cases of exophthalmic goiter without tumor are not so very uncommon. (6) It seems

unreasonable that the depressant condition of acute thyroiditis, acute infectious fevers and shock could produce increased functional activity of the thyroid. (7) Similar metabolic disturbances are present in both hyperthyroid and hypothyroid conditions. (8) The blood picture of exophthalmic goiter is practically identical with that of myxedema and cretinism.

Janney therefore advances the *"hormone hypothesis"* of thyroid toxemia and exophthalmic goiter. "If we then discard the hyperthyroid theory we have but one remaining explanation—*'dysfunction'* of the thyroid as the cause of exophthalmic goiter." He considers that the symptoms of the disease can be divided into two groups: (1) the toxic symptoms; (2) the symptoms of thyroid deficiency. Under the former he includes psychic stimulation, tremor, tachycardia, lability of the sympathetic nervous system, loss of weight and nitrogen, increased basal metabolism and tendency to rise in temperature. Under the symptoms of thyroid deficiency Janney includes the goiter, the atrophy and pigmentation of the skin, scleroderma, brittleness and loss of hair, trophic nail changes, abnormal deposition of the subcutaneous fat, imperfect ossification and epiphyseal union, fatty degeneration of the heart and body musculature, mononucleosis, delayed glucose assimilation, creatinuria, and growth disturbances in youthful cases.

The toxic symptoms are traced to the thyroid hormone itself and are probably due to the development of toxic products of its metabolism. All evidence tends to indicate that the thyroid hormone is a synthetic product —inorganic iodin and other substances possibly related to the indol-containing amino-acid tryptophane. It is possible that one or more of these intermediate substances is toxic and even identical with the products arising in the breakdown of the hormone in the body.

According to this hypothesis there is, therefore, a toxic substance present in the thyroid and blood of exophthalmic goiter patients. Janney admits that, while it seems adequately to explain most of the facts in view of our present knowledge, it too is lacking in proof.

We also feel that the dysthyroidism hypothesis has come to stay and that it is much the most rational explanation yet advanced of all the phenomena of exophthalmic goiter. Yet it is not one generally accepted by the medical profession and we have restricted the term to a group of cases in which a *disturbed* function of the thyroid secretion is more in evidence than symptoms of a purely hyperthyroid nature.

The Neurogenic Theory.—Long before the thyroid or the sympathetic nervous system were emphasized, Geigel, according to Fitzgerald, assumed lesions in the oculopupillary and vasomotor centers of the cervical cord—the former in a state of irritation and the latter in a state of paralysis. Sattler, however, assumed a lesion of a circumscribed portion of the vasomotor center or possibly a still more central portion of the brain,

which presides over the vasomotor nerves of the thyroid gland and of the intraorbital tissues; he infers from the very great constancy with which the two symptoms of goiter and exophthalmos are found combined, that the portions in question must be situated exceedingly close together. This *central or medulla oblongata* theory was strengthened by the experimental work of Filehne, who noted after injury to the restiform body in a rabbit, symptoms suggestive of exophthalmic goiter; namely, tachycardia, goiter and exophthalmos. Moreover, according to von Leube, an affection of the medulla oblongata as the original cause of Graves' disease is favored by the clinical experience of the nuclear paralyses which have been positively demonstrated in the course of the disease, of the spasms, the paralyses and atrophies of the musculature, the melituria, etc. In one of von Leube's cases of "exquisite Graves' disease," there existed besides spasms, in all four extremities, slight disturbance of the hypoglossal nerve and dysphagia. However, all must admit that the autopsies performed on the bodies of patients succumbing to Graves' disease have given, as yet, very few positive findings regarding anatomically demonstrable changes of the medulla oblongata, while the absence of symptoms of Graves' disease in various affections of the medulla is the rule. If, therefore, we are not satisfied with the assumption of a functional bulbar disturbance, in the conception of a neurosis similar to chorea and epilepsy, we must admit that the theory of the medulla being the causative factor is by no means satisfactory.

Marie (*a*) points out the fact that Filehne's rabbits do not show Graves' disease any more than the experimental production of glycosuria by puncture of the floor of the fourth ventricle is to be considered true diabetes mellitus. Further, these central findings in the medulla, etc., are not constant and are no longer considered as of importance. For want of a better theory Marie and the French school considered exophthalmic goiter as a *general neurosis,* and held that while paroxysmal diarrhea, the bulimia, the vomiting, anginoid pain, polypnea, cough and the cutaneous symptoms can all be explained by alteration of the vagus or sympathetic nerves, this is not alone the cause.

For many years an *affection of the cervical sympathetic ganglion* was generally considered as the cause of exophthalmic goiter. It had apparent support from both the pathological laboratory and the clinic. It does not, however, satisfactorily explain even the occurrence of the cardinal symptoms in that, unless we proceed very artificially in the diagnosis, we must assume for the different fibers of the sympathetic nerve either paralysis (with consequent dilatation of the vessels and development of goiter) or permanent irritation (with consequent tachycardia, palpitation and exophthalmos to some extent) or functional integrity of the fibers which cause dilatation of the pupils. Leube prefers the medullary theory to this idea of an affection of the sympathetic system.

Murray states that the sympathetic nervous system theory is not tenable, owing to, first, the absence of a dilatation of the pupil in exophthalmic goiter; secondly, the impossibility of a continuance of an irritative lesion for years, and, lastly, the absence of any demonstrated pathological lesion in the sympathetic ganglia in the majority of the cases. Nevertheless, quite recently L. B. Wilson (*f*), of the Mayo clinic, from his experimental production of lesions in the cervical sympathetic ganglia of nineteen goats by electrical stimulation and direct bacterial inoculation, concludes that "it would appear that irritation from the presence of certain bacteria within the cervical sympathetic ganglia of the goat, may produce histological pictures within the ganglia and in the thyroid, which parallel those found in the various stages of progressive and regressive exophthalmic goiter. The evidence supports the suggestion that in exophthalmic goiter the thyroid receives its stimulus to overfunction through its nerve supply and as a result usually of a local infection in the cervical sympathetic ganglia."

From the writings of Eppinger, Falta, and Hess it is evident that changes that cause irritation in some portion of the vegetative nervous system are held by many to be the underlying cause of exophthalmic goiter. Some would go further and state that this is a *sine quâ non* for Graves' disease, while a local disease of the thyroid will result in the clinical picture of hyperthyroidism, but without any of the sympatheticotonic features of Graves' disease. The stimulus, according to L. F. Barker, may be any of the previously mentioned predisposing factors, namely sinus infections, tonsillitis, pulmonary or gastro-intestinal or urogenital disease. Barker (*b*), however, states that "my own studies indicate that hyperthyroidism has no unitary origin but may be the result of changes in different parts of the body."

Biedl has come to the conclusion that the neurogenic theory was based upon inconclusive experiments and isolated, contradictory post-mortem data. Before leaving the neurogenic theories we must briefly refer to Crile's (*a*) (*b*) *Kinetic theory.* The kinetic theory is without doubt the most romantic as yet advanced. Crile points out that a true hypothesis of the pathogenesis of the disease must surely account for the lesions of both the nervous system and of the thyroid gland. In his opinion auto-intoxication and infection, as well as the thyrogenic and neurogenic theories fall short of a true hypothesis, though he admits that in the gross pathology there is a practical agreement between the nervous system and the thyroid. To quote Crile's (*b*) own words: "Graves' disease is not a disease of a single organ or the result of some fleeting cause, but is a disease of the motor mechanism of man, the same mechanism that causes physical action and that expresses the emotions; its origin is in phylogeny and its excitation is through either some stimulating emotion, intensely or repeatedly given, on some lowering of the threshold of the nerve receptors, thus establish-

ing a pathological interaction between the brain and the thyroid. This pathological interaction may be broken by diminishing the thyroid output, thus allowing the brain to regain normal control, or by securing physiological rest, which simultaneously secures normal control of the brain, which in turn will give the thyroid the opportunity of returning to the normal." . . . "Because the conception here presented relates wholly to the *release of energy* it is designated the 'Kinetic Theory.'" This romantic theory is of great interest and merits some consideration coming as it does from such a well known student of the disease. To most of us, however, it appears too theoretical and lacking in scientific confirmation. In conclusion, we would only agree with Barker that there are many and diverse causes of exophthalmic goiter; some, like sex, habitat and heredity, are predisposing; others, like shock and worry, *may* precipitate a latent hyperthyroidism; while infection may act as a direct exciting cause in some cases. The pathogenesis is not always the same; it may be of nervous, toxic, infectious or metabolic origin. A more exact statement is not possible in the present condition of our knowledge.

Symptomatology.—The symptoms are manifold and involve every system in the body, but the five cardinal symptoms are: (1) the goiter, (2) the exophthalmos, (3) the tremor, (4) the tachycardia, and (5) the increased metabolism. The relative frequency of these five main symptoms is as follows: Tachycardia in 100 per cent, tremor in 99 per cent (Sattler), struma in 96 per cent, increased metabolism in 88 per cent (A. Kocher), and exophthalmos in 77 per cent (Pende). Barker (*b*) attempts to classify the various symptoms apart from (i) the struma, under: (ii) those referable to disturbances of autonomic innervation; (iii) disturbances of metabolism; (iv) disturbances of the endocrin glands other than the thyroid; (v) cerebral and (vi) hematopoietic disturbances.

While admitting that this subdivision entails some repetition and is by no means ideal, we have adopted it in this article as perhaps the most useful in our present state of knowledge, or rather of ignorance, of the many-sided disease.

The Goiter or Struma

Size.—The thyroid gland is nearly always enlarged, though in general the enlargement is not great. G. R. Murray has classified this enlargement as: (1) slight, when the gland can be distinctly felt; (2) moderate, when it can be seen and felt; (3) considerable, when it is obvious and disfiguring, and (4) enormous, when it more nearly approaches the endemic goiter. The majority of the cases fall under the first two groups; about one-sixth are of considerable size: the enormous goiters are extremely rare, though Murray (*d*) reported one case in which the neck measured twenty-three inches in circumference and Dock (*a*) another of nineteen

and one-half inches. It must be borne in mind that careful and repeated measurements of the circumference of the neck will reveal spontaneous alterations in the size of the gland. In some cases no enlargement can be made out in spite of the most careful palpation of the neck at the time of the first visit. Thus Murray (*b*) (1896) notes a complete absence of the struma in 29 of 283 cases collected from the literature: he pointed out in this article that a closer examination would have revealed a struma in all: nevertheless in his own personal series of 120 cases published six years later the thyroid enlargement was present in only 117 cases—a much higher proportion, it is true, but still not a perfect one. Repeated examination throughout the course of the disease would probably still further reduce these figures. Barker points out that "when symptoms of Graves' disease are present and the thyroid does not seem to be enlarged, the explanation may lie in (1) a struma not recognizable before operation, (2) an insular change in the gland, or (3) an intrathoracic struma." The thyroid enlargement may be so slight as to be masked clinically by the subcutaneous fat of the neck but sufficient to be readily recognized when the gland is freed from its bed by the operative procedures. By an "insular change" in the gland is meant the occasional restriction of the hyperplasia to islands scattered throughout the normal gland substance. It must further be borne in mind that there is no necessary relation between the intensity of the symptoms and the size of the gland and that in some of the most severe forms of the disease thyroid enlargement is inconspicuous.

Shape.—The struma of Graves' disease may involve uniformly the whole gland and so give rise to a horseshoe shaped goiter or to the so-called "butterfly gland." Again one lobe may be more enlarged than the other, and this is especially true of the right.

Consistency.—The surface of the gland feels granular. There may be tenderness at the onset of the thyroid enlargement or during a temporary increase in size. Lian has recently called attention to a well defined hyperesthesia and hyperalgesia which are present over the thyroid gland in the early stage of exophthalmic goiter; indeed, he considers it pathognomonic in the larval forms. The consistency of the gland is rarely hard; more often it is firm and elastic, soft and elastic or soft. Sometimes it is so soft as to resemble a varicocele. Before we leave the physical consideration of the struma, it must be recalled that the subjects of old simple goiter may develop the clinical syndrome of Graves' disease, in which case the size, shape, and consistency of the gland differ considerably from the pure hyperthyroid goiter; thus the gland may be of a large size and is usually asymmetrical: it may be hard or soft, cystic, adenomatous or fibrous.

Vascular Phenomena.—In many cases there is a *visible pulsation* in the lateral lobes, sometimes transmitted from the carotid arteries. Some-

times the veins over the goiter show marked pulsation or the whole goiter yields an expansile pulsation, a condition termed the "struma vasculosa." In many cases there is a more or less distinct *thrill* over the enlarged lateral lobe but more usually at its upper pole. On auscultation over the four poles of the gland there is invariably a *systolic bruit,* sometimes both a systolic and a *diastolic bruit;* less frequently in the soft vascular struma one can detect a continuous murmur with a systolic intensification resembling the "bruit du diable" or even the humming top murmur of an arteriovenous aneurism. The best method of bringing out these murmurs, according to Guttmann (quoted by Moebius), is to draw the head to one direction and to listen over the convex side of the neck. The systolic murmur varies in character from a soft blowing to a musical twang or squeak, fancifully named by Fuller the "sleigh-runner murmur." Guttmann believes this systolic murmur is of arterial origin, due to the hypertrophy of the left ventricle and the uneven dilatation of the arteries in the gland.

The diastolic bruit has partly a venous and partly an anemic origin. These murmurs may be absent from the thyroid for varying periods but never depend upon the propagation of the heart murmurs which are so frequent in this clinical syndrome.

Pressure Symptoms.—The hyperthyroid goiter rarely if ever causes pressure symptoms, except of course when a hyperthyroidism becomes engrafted on an old goiter, in which case there may be pressure on the trachea or nerves, varying in degree with the size of the goiter.

The adjacent cervical *lymphatic glands* are often slightly hypertrophied and may suggest an inflammatory or even a malignant process. The true explanation, however, is usually that this adenopathy is a local expression of the tendency to a generalized lymphatic hyperplasia which occurs in this disease.

Intrathoracic Struma.—This condition deserves a brief consideration. According to Woelfler it occurs in 6.7 per cent, and to Kocher in 9.7 per cent of cases of simple goiter. C. H. Mayo states that an intrathoracic or substernal goiter is found in his clinic once in forty operations for simple goiter. The question that is naturally of more importance is: How often does an intrathoracic struma develop hyperthyroid symptoms? "Intrathoracic struma" is a diagnosis frequently made by the general practitioner in cases which, however, more correctly belong to the small almost imperceptible cervical struma. In a clinical experience of twenty years we have never seen a case in which this question has been raised. A careful search of the Surgeon General's Catalogue revealed some fourteen papers dealing with intrathoracic struma: of these the article by Wuhrmann was the most complete and dealt with ninety cases collected from the literature up to the year 1896: in none of these is a reference made to the clinical syndrome of Graves' disease, though in one case there was a

double exophthalmos, in another unilateral and occasional exophthalmos, while in five cases some palpitation or other cardiac nervous symptom was manifest.

Very recently Leiner reported a case of Graves' disease in which at one time there was a palpable struma and all the classical symptoms, but three years later there was found no cervical goiter but an area of retrosternal dullness, a positive radiogram of an intrathoracic tumor, and symptoms of slight hyperthyroidism. To make a diagnosis of Graves' disease with an intrathoracic struma one must have, in addition to the other symptoms of hyperthyroidism, clinical evidence of substernal pressure, a definite area of retrosternal dullness on percussion, and a well defined shadow in the röntgenogram. An enlarged thymus can give the two latter phenomena, hence the diagnosis is at best risky. Of course we would not accept as an intrathoracic struma a mere extension of the cervical thyroid into the thorax, as was reported by Samuel West (*a*) in two of his thirty-eight cases. The probable explanation of the rarity of true hyperthyroidism in the intrathoracic struma is the well known clinical fact that this type together with "les goiters plongeants" belong to the atoxic non-hyperplastic group and not to the so-called toxic hyperplastic goiter which is characteristic of Graves' disease.

Disturbances of the Autonomic System

Under this heading we would include all the symptoms due to an abnormal stimulation of smooth muscle, heart muscle and the secretory glands: possibly one should also include some of the metabolic disturbances, but for convenience's sake these will be discussed under a separate heading. The "abnormal autonomic innervations," following Barker's example, will be considered regionally as: (1) ocular, (2) cardiovascular, (3) cutaneous, (4) digestive, (5) respiratory, and (6) urogenital.

In both simple hyperthyroidism and in the Graves' syndrome, the sympathetic as well as the craniosacral or vagal systems are involved. When the symptoms referable to the sympathetic system predominate Eppinger, Falta and Hess speak of the picture as "sympathicotonic," while in the event of the craniosacral autonomic (parasympathetic) symptoms predominating, the syndrome is termed "vagotonic." Again when the vagotonic and the sympathicotonic symptoms are equally present, the picture is described as "mixed."

The Major Ocular Signs.—*Description of the Major Ocular Signs.*—While only a protrusion of the eyeballs was noted in the first cases described, there are now no fewer than fifteen more or less important ocular signs or symptoms. Most of these are of autonomic origin, though it

must be admitted a few have another etiology. Let us now consider each in detail.

Protrusio Bulborum.—Though protrusion of the eyeballs was noted by Parry (*a*) (*b*) as early as 1815 in one of his eight cases, the credit of emphasizing its importance as a diagnostic sign is due to Basedow (1840). To quote the latter's description: the eyes "were so pushed forward that one saw three lines wide of sclerotic below and above the cornea: the eyelids were widely separated and could not be shut with the greatest effort and the patient slept with wide open eyes." Further on Basedow describes them as like "crab's-eyes" or "Glotzaugen."

The protrusion is best seen by examining the profile of the patient, and is occasionally so great that the eyelids cannot voluntarily be closed, nor do they meet during sleep. It may be so slight as to be hardly perceptible even to the trained observer. Various attempts have been made to determine the degree of protrusion. Neumann, quoted by Murray, has estimated that the diameter of the globe is actually increased by one-tenth. It may or may not be accompanied by Dalrymple's sign or widening of the lid slits. It is usually bilateral but may be unilateral or at least more marked on one side than on the other, which is true of one-seventh of the cases, according to Wilbrand and Saenger. Unilateral exophthalmos, however, is relatively rare, as Falta (*b*) was able to collect only 109 cases from the literature and to add one himself. If there be a difference between the two sides, the protrusion is usually more marked on the side corresponding to the more enlarged lobe of the thyroid. Dock (*b*), however, states that in some cases there is goiter on one side and exophthalmos on the other. In any event protrusio bulborum is by no means a constant sign and, according to Barker, does not occur in more than 33 per cent of the cases of Graves' disease. Other authors give a much higher incidence (W. G. Thompson in 64 per cent of 80 cases, Wilbrand and Saenger in 69 per cent of 39 cases, Murray (*e*) in 70 per cent of his second series of 170 cases, and 72 per cent on his first series of 114 cases). The disparity is due no doubt to a confusion of the term "exophthalmos" with ocular phenomena other than pure "protrusio bulborum."

The protrusion is usually a late manifestation of the disease but it may have existed for years in some members of a hyperthyroid family, before the complete clinical syndrome is manifest. Again it may develop very suddenly in the very acute cases of hyperthyroidism. At first the eyeball can be pushed back by gentle pressure, but later on the eyeball is fixed in its protruded position by the fat tissue in the orbit. Barker insists that "protrusion of the eyeball" should be distinguished from a mere widening of the lid slits (Dalrymple's sign). The term "exophthalmos" has been applied loosely to one or the other, but he believes should be more correctly restricted to the actual protrusion of the eyeballs. It is of course not peculiar to Graves' disease; it occurs in high degrees of

myopia and, when more marked, in arteriovenous aneurisms, cellulitis and tumors of the orbit as well as in patients with atheroma and dilatation of the arteries and in chronic cyanosis of the head. Mueller has also reported its occurrence in some cases of lead poisoning as resulting from a toxic vasomotor condition.

Dalrymple's Sign.—Widening of the lid slits or palpebral fissure was first described by Dalrymple in 1849, according to his friend W. W. Cooper, though we could not find the original reference. It may be noticeable when the eyes are at rest but is best seen when the patient suddenly fixes his eyes on an object held before him; then the upper lid is distinctly retracted with a resulting exposure of the sclera above and below the cornea. This sign is quite independent of the protrusion of the eyeballs, but when present with slight protrusion, it may exaggerate the degree of the latter. By some writers the term is reserved for the sudden widening of the lid slit on fixation of the eyes and would not include the widening when the eyes are at rest. It is not peculiar to exophthalmic goiter but occurs in maniacal conditions, hysteria, orbital tumor, tabes dorsalis, tetanus and pregnancy; in certain cases of myocardial disease it is sometimes noted with a peculiar staring of the eyes resembling the Stellwag sign.

A true Dalrymple sign, though wrongly called Stellwag's sign by Murray, was present in 47 of his first 76 cases (or 61.5 per cent), and in 70 of his second 125 cases (or 56 per cent).

Stellwag's Sign.—Though Stellwag's name has been wrongly associated with widening of the lid slits by even such masters as the late Sir William Osler, the sign should imply the rarity and incompleteness of involuntary winking, which Stellwag states in his excellent paper of 1869 has nowhere been previously described, but which he considers to be among the most constant and even the most characteristic signs of exophthalmic goiter. It must be admitted that Stellwag also discusses in this same article the widening of the lid slits amongst the ocular phenomena of Graves' disease, but so has nearly every writer since 1849.

While normally involuntary winking occurs from three to ten times per minute, in Graves' disease it occurs much less frequently, sometimes only once in several minutes. Furthermore, in this disease each act of winking is not as complete as in health. The sign is said by Barker to occur in from thirty to fifty per cent of the cases.

Von Graefe's Sign.—Barker defines this sign as "a disturbance of the associated movement of the upper lid with the eyeball on looking downward, so that the lid does not follow the eyeball down as normally, but is held back owing to an abnormal tonus in the levator muscle." It was described by von Graefe (*b*) in 1864 as "a loss of coördination between the lid movement and the raising and lowering of the plane of direction." It is a very frequent sign, especially if carefully looked for, even in

cases without other symptoms or signs of hyperthyroidism, though it is well to warn the inexperienced clinician against laying too much stress on this sign in the absence of other symptoms of the disease. It is generally bilateral but a unilateral manifestation has been reported by Hitschmann, Friedenburg, Long and Pringle. As far as the incidence of the sign is concerned this varies greatly: no doubt *pari passu* with the care with which the sign has been looked for. Thus Hill Griffith reports it positive in 13 per cent, West in 14 per cent, Paessler in 17.6 per cent, Murray in 34 to 40 per cent, Dock in 50 per cent, and Lewin (quoted by Wilbrand and Saenger) in 55.5 per cent. As has been already stated it is sometimes present in healthy persons but has also been noted in Thomsen's disease.

Moebius' Sign.—Moebius (*a*) first noted that when a patient with Graves' disease is looking straight before him at the examiner's finger, he is unable to converge the eyes as the finger is gradually moved nearer, and one or other eye will soon deviate outward, leaving only one eye looking at the finger. The patient, however, denies the sensation of diplopia. The best method of inducing this sign is by directing the patient to fix his eyes on the ceiling and then quickly on the examiner's finger. Many cases of hyperthyroidism reveal this insufficiency of convergence, but it must not be forgotten that one also meets with it in myopia of more than ten diopters and in neurasthenic conditions other than hyperthyroidism.

Joffroy's Sign.—In 1893 Joffroy described in four cases the following sign (we quote his own words): "If one asks some one who is looking down to look quickly upwards to the ceiling, holding the head immovable, one notices that at the same time as the ocular globe executes a movement upwards, the eyebrows are elevated and the forehead is wrinkled: it is a synergic movement produced in the normal and absent in this patient whose eyebrows and forehead remain absolutely immobile, even when she makes a considerable effort to look up." The patient that he was demonstrating was, needless to say, one of his four cases of exophthalmic goiter. "One must not conclude that there is a true paralysis of the frontal muscle but rather a dissociation of the reflex movement of the muscles of the forehead and eyebrows." This sign is not noted by Mackenzie in his article in Allbutt and Rolleston's System, nor by Dock in Osler and McCrae's System. It is a relatively frequent ocular sign, though we have no figures as to its exact incidence.

Suker's Sign.—Suker states in his article, 1917, that "after extreme lateral rotation of the eyes either to the right or to the left, with the head fixed and with fixation on an object at this point maintained for a second or two, on attempting to follow the fixation point as it is rapidly swung into the median line, one of the eyes (it may be either) fails to follow the other in a complementary manner into proper convergence and fixation for this point when it is brought into the median plane. Either the right or the left eye makes a sudden rotation into the fixation with

its fellow but before it does so an apparent divergent strabismus is momentarily manifest." The object should be held three to four feet from the patient to avoid too great an effort at convergence. In other words, the author states it must be held much beyond the point usually necessary in testing for Moebius' sign. This lack of complementary lateral rotation is also more marked the greater the exophthalmos. The divergence of the eyes is a more or less jerky one. Care must be taken to exclude esophoria or exophoria and the possible presence of a paresis of the lateral rectus muscles. The author found the sign as frequent as the von Graefe and Moebius signs but gives no figures as to its frequency nor are there as yet any available in the literature.

Pathogenesis of the Major Ocular Signs.—Heinrich Mueller in 1859 gave a brief description of three groups of plain muscle fibers, one bridging over the infra-orbital fissure and one in each eyelid extending vertically from the fornices of the conjunctivæ to the superior and inferior tarsal plates respectively. Merkel and Kallius have failed to confirm Sappey's rather indefinite description of two bands of plain muscle lying one on either side of the eyeball and termed by him "internal and external orbital muscles." It has been suggested in the past that a spastic condition of Mueller's three muscle bundles, with or without weakness of the orbicularis muscle, was responsible for the ocular phenomena in Graves' disease. Their obvious inability, both from their size and position, to produce the exophthalmos, as well as the inadequacy of the older theories, such as a widening of the retrobulbar veins from a vasomotor paralysis, as suggested by Sattler and Buschan, chronic passive congestion and edema, and an increase in the amount of the retro-orbital fat (Murray) led to further investigation. The experiments of Benard in 1882 showed that by irritation of the cervical sympathetic, the eyeball is pressed forward and to a certain degree, the closure of the eyelids is prevented. Wiener (1868) showed that irritation of the cervical sympathetic ganglion caused increased intra-ocular tension, whilst its destruction caused a lower tension for a time. In 1904 MacCallum and Cornell, having removed the roof of the orbit and the orbital fat in dogs, electrically stimulated the cervical sympathetic and noted peristaltic waves passing backward throughout the tissue surrounding the eyeball and eventually great exophthalmos. By careful dissection and histological examination they demonstrated the presence of plain muscle fibers forming a smooth conical mantle about the eye, continuous anteriorly with the muscle of the lids and forming abundant attachments about the orbital margin and passing backward, thence to end about the foramen, through which the optic nerve enters the orbit. Landstroem, in his inaugural dissertation of 1907 (which has been carefully reviewed in German and American literature), reports the demonstration of a well developed cylinder of plain muscle arising from the septum orbitale, anteriorly, and inserted

just posterior to the equator of the ball. Bearing in mind the attachments of the plain muscle described by Landstroem, we must admit that the eye signs become readily explainable: thus a spastic condition of the muscle would have as its first effect a widening of the lid slit or Dalrymple's sign: the free movement of the eyelids being thus interfered with, an incoördination of the movements of the eyeball and lids would result (von Graefe's sign). The superior and inferior tarsal muscles running vertically in the lids doubtless plays a considerable part in the production of both Dalrymple's and von Graefe's sign.

Protrusio bulbi is produced when the hypertonicity of the plain muscle overcomes the tonus of its antagonistic recti muscles. Convergence of the eye increases the distance between the origin and insertion of the mesial portion of the cone of plain muscle, which is, as a result, well developed to meet this oft-repeated act. A spastic condition of the plain muscle would tend to overcome the tonus of its antagonist—the internal rectus—and a break in convergence would result (Moebius' sign).

Landstroem's findings and conclusions were subsequently challenged by a fellow countryman, Troell (*a*), who, in his first paper in 1914, raised the following objections: First, that the Landstroem muscle is so weak and so asymmetrically placed as to be hardly capable of producing the eye signs alone. Secondly, it is above all difficult to understand how a contraction of that muscle should produce a pronounced shifting forward of the posterior *origin* and thus of the entire eyeball and not a shifting back of its anterior origin, since the former is a point considerably more fixed than the latter. Thirdly, even granting the possibility of the above forward movement and assuming that the contracted condition of the muscle is the result of a stimulation of the sympathetic fibers, how can one account for the ocular signs being unilateral in 10 per cent of cases and pupillary signs not being part of the syndrome and only occurring twice in his series of 164 cases? Troell (*b*), however, believes it wise to offer no theory as a substitute for Landstroem's, but proceeds to experimental investigation, the results of which he published in 1916. He succeeded in producing exophthalmos and the lid phenomena in dogs by the subcutaneous injection of paraphenylenediamin hydrochlorid and that even after one sympathetic ganglion had been removed. Troell finally admits that the problem of the production of the ocular signs of exophthalmic goiter remains unsolved.

Finally one must consider what produces an increased tone in the various muscle bands of Mueller and Landstroem. It is generally assigned to a sympatheticotonic response. Long ago Fr. Mueller considered the probability of some action of the thyroid gland upon the sympathetic ganglion in the neck, as suggested by two cases of unilateral exophthalmos in which there was goiter on the same side; in one of the two, the goiter, and at that time also the exophthalmos, had been bi-

lateral; finally, after one side of the thyroid was removed, the exophthalmos disappeared on that side. These observations were of course very suggestive and are usually quoted by those who regard the *protrusio bulbi*, Dalrymple's, Stellwag's, von Graefe's and Moebius' signs as the result of stimulation of the sympathetic fibers. It is true that Wilbrand and Saenger mention four other possibilities for von Graefe's sign, namely central irritation, action of the orbital vessels upon the levator palpebrarum, insufficiency of the orbicularis muscle and increase of the forces that cause elevation—all purely hypothetical possibilities.

Minor Ocular Signs.—In addition to the above described six or seven ocular signs there are several of less importance.

Gifford's Sign.—Gifford in 1906 described, as an early sign, difficulty in everting the upper eyelid, on account of its retraction and rigidity. He also described swelling of the eyelids, sometimes of the upper alone and sometimes of the lower as well. It is not a true edema, as it can be dissipated by causing contraction of the orbicularis by faradic stimulation. Sometimes, however, there is a solid edema of the eyelids which remains for a long period, even after many of the other symptoms have disappeared, and probably caused by a subsequent hypothyroidism—another point in favor of the dysthyroidism theory. Suker has confirmed the first mentioned sign of Gifford.

The Glistening Eye and Epiphora.—Those due to the vagatonic symptom of increased lacrimation are not infrequent. The increased flow of tears is due to a stimulation of the autonomic fibers of the seventh cranial nerve.

Loewi's Sign.—Loewi's sign, or epinephrin mydriasis, is due to a heightened tonus of the dilator pupillæ muscles. The test consists in the instillation of a few drops of a 1 to 1000 epinephrin solution into the conjunctival sac; this is followed by a dilation of the pupil. The sign is also occasionally positive in diabetes mellitus. This phenomenon, together with *the dry eyes* from lessened lacrimation, are sympathicotonic phenomena. Sometimes *ulceration of the cornea* results from the diminished secretion and the lessened sensitiveness of the cornea, according to von Graefe and Jessop, even in patients not severely ill. It is more frequent in the male than in the female, probably from increased exposure. This ulceration may go on to actual sloughing of the cornea, perforation, panophthalmitis and destruction of the eye. In Mackenzie's case the perforation occurred quite painlessly and the eye was lost before the patient made any complaint about it. C. H. Mayo has observed two patients totally blind from this cause and several patients blind in one eye.

Anisocoria.—Anisocoria or inequality of the pupils is due to a disturbance of balance between the sympathetic and vagal autonomic nerve supply of the pupillary muscles on one side. It occurred in only two

patients of Troell's (*a*) series of 164 cases, but has been observed also by Claiborne. The latter in addition calls attention to the dilatation of both pupils in advanced exophthalmic goiter and particularly in the blonde subject; following thyroidectomy the pupils become smaller.

Jellinek's Sign.—Pigmentation of the eyelids is due in all probability to an associated disturbance in the chromaphil system. It is generally part of a widespread pigmentation; it is an early symptom and diminishes usually during the course of the disease.

"Riesman's Sign.—*A loud bruit* audible over the eyeball has been noted by Riesman in two cases of Graves' disease with especially marked vascular phenomena. A search through the literature revealed the fact that it had been previously described by Donders, Schoenfeld and Carrington and Drummond.

Rosenbach's Sign.—This consists of tremor of the closed eyelids and is of course part of the generalized muscular tremor.

Paresthesias.—Subjective feelings of heat or pain in the eyeballs are not uncommonly complained of, just as in other parts of the body. Paralysis of the various ocular muscles, nystagmus, etc., will be considered under the nervous symptoms and the complications of the disease.

Cardiovascular Symptoms.—The circulatory system suffers more than any other system in exophthalmic goiter. Its condition determines very largely the course and the prognosis of the disease. The "Kropfherz" of Kraus and the "cardiopathia thyreogenes" of His are terms used to designate the cardiac symptomatology of Graves' disease and simple hyperthyroidism.

Tachycardia.—Tachycardia, which is also known as pycnocardia, polycardia and syncosphyxia, is the most constant sign of Graves' disease, occurring, as it does, in practically 100 per cent of all cases, according to Murray and many other authorities. In well marked cases the pulse rate may range between 100 and 180 or even 200 beats per minute. In one of Dock's cases it reached 225 beats and continued at this rate for many hours. According to Mackenzie (*b*) the rate in mild cases varies from 90 to 110, in moderate cases from 110 to 130, and in severe types of the disease from 130 to 160 beats per minute. According to Kocher the pulse falls to 80 beats per minute only after a long rest. While physical exertion increases the tachycardia, an emotional stimulus does this to a still more marked degree. It is often the first symptom of the disease; in fact, all pulse rates that remain persistently above 80 to 85 beats per minute should be regarded as a suspicious symptom of Graves' disease in the absence of an acute or chronic infection. Barker states that it is not unusual to see a "rest-cure" patient with an initial bradycardia of 60 to 65 beats, develop, after bed-rest and overfeeding, a tachycardia of 80 to 100 beats through the unmasking of a thyropathy, often responsible, in part at least, for the so-called nervous breakdown. Mueller be-

lieves "the hyperthyroid heart can be distinguished from the nervous cardiac affections by the fact that the high pulse rate lasts throughout the whole day and night and is not due to reflex action alone."

The rapid heart action is caused by a stimulation of the accelerator nerve of the heart, coming from the sympathetic nerve, by the action of the thyroid intoxication; the inhibitory fibers of the vagus may be affected but to a lesser extent; hence it is more marked in the sympathicotonic and less marked in the vagotonic cases. The mechanical origin of the tachycardia is no longer entertained.

Investigators assert, according to Bram (*c*), that the stimulation of the vagus, causing universal peripheral vascular dilatation,[1] occasions increased thyroid vascularity and increased formation of thyroid substance; the latter thrown into the blood stimulates the vagus: thus a vicious cycle is formed.

Palpitation.—This subjective sensation of the heart's action is sometimes very distressing. As is well known to students of cardiac disease, it is largely independent of the pulse rate, being often less marked in cases with marked tachycardia than in those with slight. Sometimes there is an associated feeling of suffocation or swelling in the throat. It is always a suggestive symptom of hyperthyroidism when it occurs in a person without other discoverable cause; indeed, Mueller states that "nearly a third of all cases of so-called nervous palpitation belong to this disease." This is especially true of the incomplete hyperthyroidism when only the cardiac symptoms are very prominent. In the hyperthyroid heart as well as in fully developed exophthalmic goiter, the increased pulsation is especially felt over the region of the right ventricle and at autopsy there is present a marked hypertrophy and dilatation, especially of the right ventricle.

The Heart.—The heart is often moderately dilated and may be hypertrophied from a prolonged thyroid intoxication. While the left ventricle is most affected, the right, according to Kraus, is also sometimes enlarged. In severe cases, late in the disease myocardial insufficiency may develop and lead to a fatal termination. Auricular fibrillation is a common accompaniment of this myocardial degeneration. Anginoid precordial pain may occur, according to Marie and Bram, and be severe enough to resemble true angina pectoris, particularly when associated with slight unconsciousness.

Upon physical examination the precordium is often prominent, especially when the disease has begun in early life. The whole anterior part of the chest may heave from the forcible action of the heart and the movement may be perceptible even through the clothing. The head and body may be shaken with each heart beat (Musset's sign) as in true aortic

[1] The assumption that vagus stimulation causes "universal vascular dilatation" rests upon very dubious physiological grounds.—R. G. H.

insufficiency. Palpation will reveal a pounding, violent impact and sometimes a systolic thrill or diastolic shock. Curiously enough, the clinical apex may not be much displaced, and even if far out, it can be localized in the fifth or even the fourth interspace. On percussion the dullness is found increased, especially to the left, though as a rule this increase is not proportionate to the severity of the tachycardia, palpitation or area of visible precordial pulsation. In Swan's series, 50 per cent of the patients revealed, clinically, an increased area of cardiac dullness suggestive of a hypertrophy.

On auscultation the heart sounds are usually loud but the first sound is rarely clear and of normal tone, even in the absence of a murmur. The heart sounds are sometimes audible to the patient, and often audible to the examiner without applying the ear or the stethoscope to the chest: thus Graves writes that: "In one case I could distinctly hear the beating when my ear was distant at least four feet from his chest." Reduplication of the sounds and in severe cases gallop rhythm may be present. Accidental murmurs, both systolic and diastolic, may be heard, especially over the base. Apart from these so-called "hemic murmurs," it is not uncommon to note the soft blowing apical murmur of a relative mitral insufficiency from a stretching of the right auriculoventricular ring in a moderately advanced goiter heart. The causes of the murmurs are various: no doubt muscular insufficiency is the chief factor and anemia a rare one. Sahli believes that "the systolic murmurs are arterial, depending upon the 'pulsus celer,' to be described later." It is not decided, according to Bram's quotation of Sahli, whether the diastolic murmur is arterial, resulting from the pulsus celer or whether it is a diastolic portion of the venous murmur, isolated and strengthened because the veins are compressed or closed by the arteries during systole.

There is sometimes an associated valvular endocarditis or arteriosclerosis present.

The goiter heart, though in the majority of cases due to thyroid intoxication, may sometimes depend upon pressure on the vagus nerves in the neck, when it is known as "Rose's goiter heart" or the dyspneic form of goiter heart.

Upon Fluoroscopic Study.—Bauer and Helm recognize the existence of two main groups of heart disturbances in goiter. (1) The mechanical goiter heart of Rose and (2) the thyrotoxic goiter heart which may be subdivided into (a) the irritable goiter heart originally described by Minnich and Kraus and (b) the torpid goiter heart. They believe that the fluoroscopic findings of the thyrotoxic goiter heart are characterized by (1) a prominent outward bowing of that portion of the left border of the heart which represents the pulmonary artery, (2) an active pulsation of the entire left border of the heart, (3) a high, narrow aortic shadow,

and (4) a blunt apex so that the transverse diameter may not exceed the normal and is often less than normal.

The Arteries.—The carotids and brachials may pulsate violently and the radial pulse may have the characters of the "pulsus celer" to as marked a degree as in aortic insufficiency. Folley has noted the marked pulsation and even dilatation of the abdominal aorta, as well as of that of the ascending portion of the arch, which can be well seen in the fluoroscope and which has been called by him the "see-saw sign." This pulsation of the abdominal aorta is especially annoying to some patients.

Further as a rule in these cases a well marked "capillary pulse" can be seen in the nail bed, the mucous membrane of the lips, the retinal vessels, especially of the optic disc and at the margin of the red line which appears upon stroking the skin of the forehead. The venous pulse in the veins of the hand may be seen with great distinctness. The sphygmograph, or better still the polygraph, will reveal in addition to the pulsus celer a "pulsus irregularis respiratorius." Arhythmia is not uncommon but is usually of the ventricular extrasystole variety. In other cases there are more marked arhythmias, as the nodal or even the pulsus alternans. In some cases there is irregularity of force and rhythm leading to a slow pulse count at the wrist.

The electrocardiogram shows a tracing exactly similar to that obtained following physical exertion. Barker and Richardson report a case of hyperthyroidism or perhaps dysthyroidism in a patient with focal infections and thyroid adenomata, whose electrocardiographic study revealed at one time or another (1) a physiological rhythm, (2) a dislocation of the pacemaker from the sino-atrial node to points elsewhere in the atrium, (3) alternate atrial extrasystoles, paroxysmal tachycardia and atrial flutter.

White and Aub noted in a routine electrocardiographic study of 47 cases of hyperthyroidism, auricular fibrillation in 6 patients (13 per cent) and paroxysmal auricular flutter in one. While some patients have been observed to have an irregular pulse for years without evidence of cardiac decompensation, the severe arhythmias are usually of serious prognosis. Occasionally a venous pulse has been noted in the liver and spleen in acute cases of Graves' disease.

The Blood Pressure.—The blood pressure is said by Barker (*b*) to be usually too low, though he admits that "the Graves' syndrome may occur also in patients with arterial hypertension." Such a statement is quite contrary to the experience of the writer, who has for years been struck with the constancy with which a slight increase in the systolic pressure (130-150 mm.) is present even in moderate cases of hyperthyroidism when first coming under observation. Our observations are in accord with those of Dock, Plummer and Swan in this country and such continental clinicians as Pierre Marie (*b*), Kraus, and A. Kocher (*b*). Dock (*a*)

believes that the widespread opinion that the blood pressure is low is due to the quick pulse, which in many cases seems to the touch that of low tension; this quick pulse, he points out, depends upon a large pulse-pressure. Dock noted in almost 60 per cent of his patients a systolic pressure above 130 mm. of mercury.

Kraus believes that the blood pressure varies greatly in exophthalmic goiter but is usually increased slightly above normal and responds more rapidly to stimulation than does the pressure of a normal individual. Orth noted a high blood pressure in seventy per cent of his goiter patients, which after thyroidectomy fell below normal, but gradually righted itself in a few weeks. According to Plummer (*c*), in 117 cases which were more than forty years of age, 47 per cent had a systolic blood pressure above 150, and 34 per cent above 160 mm. of Hg. Even if one looks at his tables of percentage by decades, one finds a pressure above 160 mm. in 12 per cent in the second, 17 per cent in the third and 22 per cent in the fourth decade. This forms only a slight contrast to the systolic pressure of non-hyperplastic goiter in which 18 per cent of the subjects had a systolic pressure above 160. The percentages are distinctly lower in the first four decades, however, and form therefore a more definite contrast.

Plummer believes that the high systolic blood pressure, though transitory, is due to the same factors that later lead to high diastolic blood pressure and permanent cardiovascular changes. After studying Plummer's tables we can state that in 81 per cent of hyperplastic goiter (Graves' disease) and in 62 per cent of simple goiter in patients over forty years of age the systolic blood pressure was above 150 mm. of Hg. A fall in blood pressure may be considered indicative of cardiac insufficiency and as an unfavorable prognostic sign. "The high pulse-pressure with the well known vasomotor phenomena of Graves' disease leads to the almost unquestionable conclusion that there is no *vascular hypertension*[2] in this condition. The high systolic pressure is essential to the maintenance of a normal diastolic blood pressure in these cases having a low peripheral resistance. . . . . That the long continued intoxication associated with the hyperplastic thyroid may lead to hypertension is probable."

Finally Swan from a study of the blood pressure in fifty cases concluded "that the first effect of dysthyroidism on the blood pressure is to produce a lowering of the systolic pressure. This is accompanied by a disturbance in the pulse pressure, usually an increase. After the case has persisted for a varying period, the systolic blood pressure begins to rise, and after the development of cardiac hypertrophy and renal and vascular changes, the cases are converted into typical cases of chronic hypertension."

A consideration of the above evidence will permit the statement that,

[2] Italics mine.—C. P. H.

whatever be the cause, a very considerable percentage of cases of Graves' disease will reveal at some time or another, during their course, an increase in the systolic blood pressure.

Vasomotor Phenomena.—These are almost invariable and are best exemplified by flushing of the face or neck, transient erythemas of the upper chest, purpura, dermatographia, urticaria, pruritus, and subjective feelings of heat. These will be further considered under the cutaneous symptoms. Anginoid precordial pain has already been referred to.

The Cutaneous Symptoms.—The skin is strikingly pale, thin, soft and satiny to the touch. It is always moist and at times bathed in a profuse sweat which is always extremely annoying to the patient. The sweating, which is especially marked under excitement, while usually generalized, may be unilateral or even localized in its distribution. Du Castel refers to a case reported by Williams with profuse sweating of only the right leg below the knee. Moist hands and feet are almost invariable accompaniments of hyperthyroidism. Increased perspiration was present to some degree in 76 and to a marked degree in 55 patients of Murray's series of 120 cases. Apart from the sweating there is always a feeling of subjective warmth and a tendency to feel more comfortable during the cold weather.

Vigoroux' Sign.—The variation in the electrical resistance of tissues was first described by Vigouroux in 1879 with an especial reference to hysteria in which it was found increased. Charcot (*b*) in 1885 spoke of the lowered resistance of the skin to the galvanic current noted in the cases of Graves' disease studied in his clinic by Vigouroux. Two years later Wolfenden, of England, found from a study of 25 cases of Graves' disease that the electrical resistance of the skin may be very low (200 to 300 ohms) even in the early stage of the malady, in contrast to the normal resistance (4000 to 5000 ohms) of simple goiter. In a later paper Vigouroux (*a*) (1887) found it much reduced even in the larval cases or "les formes frustes" of Graves' disease.

The method of examination is briefly as follows. One requires a constant cell battery, a resistance coil of 100 ohms, a galvanometer graduated in milliamperes and a pair of electrodes. One should always apply the latter to the same portion of the body, namely the nape of the neck and the top of the sternum. The body resistance to the passage of a moderate current of fifteen volts will vary between 4000 and 5000 ohms.

According to both Wolfenden and Vigouroux the decreased resistance is not due to the increased moisture of the skin so common in exophthalmic goiter, for it occurs whether or not the skin be wiped dry and dusted with starch powder before the electrodes, also almost dry, be applied. It is not due to errors from the variation in the size of the electrodes, or in the variation in the strength of the current used, for both of these can be controlled. The *raison d'être* is not clear, but in Wolfenden's opinion

"it is not unlikely that the reason of this diminished resistance in Graves' disease is to be found in the vasomotor dilatation of the skin capillaries, which thus render the skin saturated with fluid and practically reduce the thickness of the ill-conducting epidermis to a minimum." Cardew, while reporting a diminished electrical resistance in 15 out of 20 cases of Graves' disease, denies its diagnostic value and assigns it to the increased sweating which may not always be perceptible to the patient or even to the examiner's hand. With this latter explanation von Leube and Barker are fully in accord.

Pigmentation of the skin has been frequently observed. Thus Murray noted it in 16.6 per cent of his first 120 cases, and in 23.3 per cent in his series of 180 cases. It may be generalized over the surface of the body but is more often localized to the eyelids, face, nipples, axillæ, genitalia and regions where pressure is caused by the clothing. The mucous membranes of the mouth and lips is rarely if ever affected. The pigmentation often fades as the other symptoms improve. Patches of leukoderma or vitiligo and multiple telangiectases may appear alongside of the pigmented areas. It is generally thought that this pigmentation is due to an associated disturbance of the chromaphil system.

According to du Castel there are many other trophic cutaneous troubles apart from the pigmentation and vitiligo, namely scleroderma, diffuse or localized alopecia, telangiectases, multiple gangrene, etc.

Scleroderma has been reported in patients with Graves' disease by Jeanselme, Dupré and Thibierge, according to du Castel. This is of interest because of the occasional response of scleroderma and morphea to the administration of thyroid extract.

Purpura, while not common, has been noted by du Castel, Maude (*c*), Dore and Burney Yeo. It is usually discrete and rarely in itself of great severity, though the hyperthyroidism is usually of a severe type.

Edema.—Millard collected nine cases from the literature up to the year 1888 and added two cases of his own. Maude (*a*) states that a slight edema of the ankles occurred in one-third of his cases. He considers three varieties of edema as of possible occurrence in exophthalmic goiter: (a) edema of cardiac insufficiency, (b) edema of nervous origin and (c) transitory edema. The transitory edema is the rarest, and is irregular, fugitive and asymmetrical in its distribution. Its favorite sites are the neck, arms, hands, cheeks and eyelids and, rarely, the supraclavicular fossæ. It may last only a few hours, does not pit on pressure, does not exude fluid to a needle prick and when present in the eyelids does not cause closure of the palpebral fissures; indeed, it may be present with retracted eyelids. This type does not yield to thyroid extract. Maude considers the intermittent hydrarthrosis, noted under "complications," as another form of this angioneurotic edema. While patches of solid edema of the skin are now well recognized as occurring in Graves' disease,

Morrow has reported a unique case in which the solid edema was symmetrical and did not yield to thyroid extract, while the skin over it presented the characteristic changes of elephantiasis. Nevertheless some of the cases of Graves' disease with symmetrical solid edema are caused by a secondary hypothyroidism or possibly dysthyroidism and will yield promptly to thyroid extract as rapidly as does true myxedema.

Dermatopathies.—*Erythema*, probably of a toxic nature, is very common, while *urticaria, pruritus, furunculosis* and *eczema* are not rare. Multiple gangrene will be considered under the complication of the Graves' syndrome.

Canities.—Early graying of the hair is said to occur, and has been seen by me in one female patient.

The nails are long and tapering, and occasionally show trophic disturbances, being thin, weak and brittle—sometimes, indeed, being represented by a soft paper-like film, comparable to a micaceous transformation. These trophic disturbances sometimes vary in the two hands and even in the individual fingers. They have been well described by Kohn, Uphoff, Kocher (*b*), Riedel, Landstroem and Stewart and Gibson.

Gastro-Intestinal Symptoms.—The *teeth* show rapid decay and marked fragility, according to Koeppen, Buschan, Mannheim and Kocher.

The Appetite.—Appetite is variable, though anorexia is uncommon except when the disease is running an unfavorable course. There is more often bulimia or a voracious appetite with an especial craving for carbohydrate food. Again the appetite may be capricious and the patient as in pregnancy have longings for unusual kinds of food. The bulimia is said to occur in two forms: in one the craving occurs at long intervals in paroxysms extending over several days; in the other the hunger occurs almost daily, usually several times a day for periods of an hour or so, though the bulimia in this variety is not as intense as in the former variety. Both types may accompany the diarrhea and vomiting, but not necessarily so. *Thirst,* too, may be increased owing to the excessive sweating.

The Saliva.—This may be profuse in the vagotonic cases or scanty in the sympatheticotonic. It may be paroxysmal in occurrence but is usually more or less continuous. Diminished salivation with a resulting xerostomia is rare.

The Gastric Secretion.—Miesowicz reports a case of complete absence of the hydrochloric acid from the fasting gastric contents, from the material removed after a test meal and from the vomitus. This observation was confirmed by him in four out of seven patients with Graves' disease that were later examined by him. Considerable amounts of mucus were found in the gastric contents of his first case. There is also reduction in the amount of pepsin. The motor function may also be affected, and premature emptying of the gastric contents as shown by the motor test

meals and barium X-ray examination. Miesowicz has observed at autopsy atrophy of the gastric mucosa.

Vomiting.—This is sometimes very troublesome in the severe cases, and may apparently be unrelated to the ingestion of food. It may be quite exhausting though is rarely if ever painful, but of course results in a more or less profound acidosis with a fruity odor to the breath, acetonuria, air hunger and restlessness. Hematemesis of a mild degree may accompany these crises. Vomiting was noted by Murray in only eleven of his 180 patients.

Diarrhea.—Diarrhea of a watery, painless character may be present, and was noted by Marie (*a*) in 12 out of 15 patients, by West (*a*) in 7 out of 38, by Mackenzie in 8 out of 38, and by Maude (*b*) in 4 out of 9 patients. These small series no doubt exaggerate its true frequency, as it was observed by Murray in only 20 out of his large series of 180 cases—an incidence of just over 11 per cent. The number of stools varies from four to thirty in the twenty-four hours. One of the writer's recent cases of hyperthyroidism was complaining chiefly of a profuse diarrhea, with ten to twenty-four stools per diem, which had led to a diagnosis of parasitic diarrhea by her previous physician and to very frequent examinations of the stools for amebæ or other intestinal parasites. It is a true "intestinal crisis" and has been aptly termed "bowel hurry" by Hingston Fox. It is often paroxysmal and has been likened by Charcot to the gastric crises of tabes dorsalis. The bowels may be quite regular for some weeks and then suddenly, usually in the early morning and without apparent cause, the patient has without pain or colic large, liquid, light-colored stools varying greatly in number. The feces resemble at times the "rice-water" stools of cholera from the small flakes of mucus present: rarely are they definitely bloody: they may show good digestion or none at all: bile is often deficient. In one of Maude's cases the attacks of diarrhea were accompanied by a rise in temperature—the first attack of which was mistakenly diagnosed typhoid fever. The diarrhea may be very intractable and lead to rapid and profound cachexia. The crises often alternate with periods of constipation of the spastic type. It may or may not be associated with vomiting. A slight melena with bright red blood may accompany the severer crises. Sometimes the diarrhea is dietetic in origin and in others it is due to a gastric hyposecretion with hypermotility: rarely it has the features of a toxic process associated with abdominal pain. Eppinger and Hess and more recently Pottenger and Crotti have assigned the diarrhea to an excessive stimulation of the intestinal glands and longitudinal muscles of the bowel by the vagus nerve —secondary to some toxic influence of the thyroid—in other words a vagotonic symptom: the same is true of the vomiting.

Steatorrhea.—Fatty diarrhea independent of the mucous diarrhea may occur, due to a disturbance of fat-absorption and not to faulty fat-

splitting from a disturbed pancreatic function. Schmidt and Salomon, as well as Falta have, on the contrary, described cases of fatty diarrhea and a lowered carbohydrate tolerance, which they have assigned to inhibition of the internal secretion of the pancreas.

Icterus.—According to Crotti "in a few cases of very severe thyrotoxicosis icterus may be observed. This icterus is rare, though it is not uncommon to observe a yellowish tint of the sclerotics in severe thyrotoxic-intestinal disturbances." The prognosis of this icterus is always bad. It indicates some degeneration of the liver and when marked is usually associated with general edema and ascites. It is not due to obstruction in the bile ducts but is of toxic origin.

Respiratory Symptoms.—While these are not frequent or important, they are of considerable interest. . They depend upon a stimulation of the visceral nerves and probably are of toxic origin.

Cough.—Cough of an irritative dry ringing character may be quite troublesome. It may or may not be associated with hoarseness or even aphonia. It may sometimes depend upon local pressure of the struma on the trachea or recurrent laryngeal nerve, though this is not as common as in colloid goiter. The usual explanation is a stimulation of the vagus; it was considered by Germain Sée as a form of laryngeal crisis.

Dyspnea.—First we must note that subjective feelings of dyspnea are often complained of by the patient without any manifest increase in the rate or the depth of the respiration. Tachypnea or rapid breathing is also reported and occurs apart from exertion. Asthmatic attacks are not infrequent. Hoffbauer and Sharp both report crises of dyspnea, associated with aggravation of all the hyperthyroid symptoms, a swelling of the vessels of the neck, cyanosis and impending asphyxia. Such attacks, according to Mackenzie, have proved fatal. Sharp was struck with the resemblance of the picture to that of atropin poisoning, which was further suggested by the remarkable response to opium. It has been supposed that they arise from a sudden increase of direct pressure of the goiter on the trachea, but Mackenzie believes it is improbable that they depend upon mechanical causes.

Hoffbauer, whose paper should be read by all, states that the respiratory disturbances cannot be explained by cardiac disease, hysteria, bronchitis, bronchial asthma or pressure upon the trachea. He believes that the experimental work with thyroid extract as well as clinical observations suggest a toxic origin in many cases, though by no means in all, when the above-mentioned factors may be considered. He took graphic records in three patients with exophthalmic goiter by means of a Knolls cardiopneumograph and a Marey drum and made the following classification of respiratory disturbances: (A) Continuous disturbances characterized by (1) leveling of the respiratory curve, (2) a simultaneous prolongation of both inspiration and expiration, and (3) irregularity of

the size and form of single elevations with periods of complete or almost complete respiratory pauses. (B) Periodic attacks of (1) deepening of the respiration, (2) more rapid inspiration and expiration, and (3) respiratory pauses.

Pulmonary Hemorrhages.—Hemorrhages from the lungs have been observed, and Murray has described crises of *bronchorrhea.*

Bryson's Sign.—Bryson in 1889 first noted a diminished chest expansion in every case of Graves' disease examined by her: this amounted in severe cases to a restriction of the chest measurements to half an inch. She believed that an expansion of one inch or more was of favorable prognosis. This phenomenon was confirmed by Hammond and named by him Bryson's sign. Patrick, some years later, reported its presence in only 10.5 per cent of forty cases and considered it in no wise pathognomonic, nor indeed an important sign. He further states that it has no significance in prognosis and should be relegated to the comparative obscurity of an individual in a large community of manifestations all of which depend alike upon the general state.

Bryson also noted in one patient a peculiar catching of the breath when reading aloud.

A disturbance of *Litten's phenomenon* often suggests imperfect contraction of the diaphragm. This as well as the diminished chest expansion may be explained by the muscular weakness which is often a marked symptom of the disease.

Laryngeal Paralysis.—Matthews concluded from a study of the vocal cords in one thousand cases of goiter that the nerve fibers supplying the abductor impulse of the posterior crico-arytenoid muscle are most readily affected by pressure of the enlarged thyroid. Thus there occurred a partial or a complete paralysis of one or both cords in 272 cases—an incidence for all types of goiter of 27 per cent. He further states that: "Exophthalmic goiter does not differ materially from other forms of goiter in its effects on the vocal cords except in cases of extreme hyperthyroidism in which the effects are evidently increased as a direct result of general muscular wasting." This paresis of the cords often occurs without hoarseness or other symptom of laryngeal involvement, and on this account Matthews emphasizes the importance of a careful laryngoscopic examination before operation. C. H. Mayo also makes a similar plea.

Urogenital Symptoms.—The intimate relation of the thyroid gland to the female genitalia has long been appreciated on account of the swelling of the thyroid at puberty and during pregnancy. Further, Graves' disease is more frequent in women than in men.

Menstrual Disturbances.—Menstrual disturbances are frequent according to some observers, while others comment on their comparative rarity. Murray noted disturbance of menstruation in 45 out of 170 cases,

or 27 per cent; amenorrhea was present in about half of these cases, though menorrhagia was also noted.

Pregnancy, Relation of Exophthalmic Goiter to.—Pregnancy may take place notwithstanding the existence of a moderate form of hyperthyroidism.

In fact, it is often rather beneficial than otherwise, though of course it should not be recommended unless the condition of the patient is fairly good and on the upward course.

The Breasts.—The breasts may show early hypertrophy in either sex or they may look virginal in middle life. This hypertrophy may be related to the lipomatosis sometimes present in other parts of the body in Graves' disease.

Nevertheless in the majority of cases the mammary glands are usually more or less atrophic. Basedow reports a male patient with swollen, hyperemic breasts, secreting colostrum.

Libido and Potentia.—These may both be lost in men. In both sexes genital hypoplasia is not infrequently associated with exophthalmic goiter, though always with a general involvement of the endocrin glands and especially with hypopituitarism.

Urinary Manifestations.—*Polyuria.*—Disturbances of urinary secretion may occur; polyuria is a frequent symptom but occasionally oliguria may be noted.

The polyuria may be explained by the increase in thirst and appetite, but in some cases a neurosis or even diabetes insipidus have been considered the cause.

Polliakuria or frequency of micturition may be quite troublesome in the course of the disease.

Albuminuria.—The kidneys are rarely severely affected but albuminuria with hyaline casts is usually present when the heart is much dilated. Begbie and others have reported intermittent albuminuria of a considerable and sometimes an excessive degree. Murray found albuminuria in six of thirty cases in which a urinary examination was made and considered it more frequent than glycosuria which occurred three times in his series.

Glycosuria will be discussed in a following section on alterations in metabolism.

Various Urinary Constituents; Relation of Exophthalmic Goiter to.—The *urea* and *uric acid ammonia* contents of the urine are the same as in health. *Acetone* has been noted in small quantities by some observers; large quantities occur when there is a relative deficiency of the carbohydrate intake or after crises of vomiting and diarrhea. *Indicanuria* does not occur, for marked putrefactive changes in the intestine are not a feature of the disease. A retention of phosphorus has been noted by Scholz corresponding to the gain in nitrogen.

Disturbances of Metabolism

In 1893 Friedrich Mueller (*a*) demonstrated a great acceleration of the metabolism in Graves' disease. Since then many investigations have been undertaken and have revealed the fact that the disturbances involve the total combustion as well as protein, carbohydrate, fat and mineral metabolism.

Basal Metabolism in Exophthalmic Goiter.[3]—The total combustion or general heat production or the "basal metabolism" of modern parlance is measured by the carbon dioxid production and oxygen consumption. The emaciation is related to the increased total metabolism and the remarkable increase of the consumption of oxygen and the output of carbon dioxid. In severe cases of Graves' disease the increase of oxygen consumption amounts to as much as fifty to seventy per cent—an increase which Magnus-Levy (*e*) states "occurs nowhere else in the whole range of pathology." Instead of three and a half to four cubic centimeters of oxygen per kilogram, Magnus-Levy found that the values may rise to four and a half, six or even seven cubic centimeters. "The fires of the body are, as it were, fanned into an intense flame," as Barker succinctly puts it. A patient having hyperthyroidism, though at rest, may use as much oxygen as a normal man at hard labor. This acceleration of the oxidative processes may strain the heat regulating mechanism, consequently slight elevations of the body temperature frequently occur.

According to Steyrer the total caloric output is definitely increased: this affects both the fat and proteid intake. The caloric production in Graves' disease is a strikingly variable one under similar feeding and other external conditions. It seems clear to Steyrer that these variations run parallel to the general nervous instability of the organism. Slight differences of body weight are scarcely noticeable and depend upon the amount of protein intake. Administration of thyroid extract, even in large doses, called forth no marked increase of the energy requirements. There exists, therefore, a remarkable contrast between the exophthalmic goiter and the myxedema patient. The increased basal metabolism is not, according to Pribram and Porges, influenced by abstinence from meat or other protein foods, but overfeeding with meat causes an increased rate. There is, therefore, no indication for a vegetarian diet. Further, in spite of an increase in the body weight, they could note no reduction of this increased metabolism from X-ray treatment over the thyroid gland. DuBois concludes that the measurements of the heat production gives us the best index of the severity of the disease and of the effect of treatment. In severe cases the warmth of the skin and the sweating can be accounted for entirely by the necessity for the increased elimination of

[3] This topic is further discussed in another chapter.

heat. At least a part of the tachycardia is due to the increased metabolism. There is evidently no interference with the oxidation of carbohydrates. The average water elimination through the skin and lungs in the severe and moderately severe cases is 39.9 grams per hour. This increase above the normal is closely proportional to the increase in heat production; 25.7 per cent of the calories are dissipated through vaporization in goiter patients, whereas the mean normal is about the same or 23.9 per cent. Means and Aub (*a*) state categorically that "while a rise may be likewise found in a few other pathologic conditions, it is less marked and is found in conditions easily differentiated from hyperthyroidism." It seems fair to say that a rise in the basal metabolism is not only a constant feature but is one of the most striking and characteristic manifestations of thyroid overactivity. This rise, therefore, may be used as a functional test of the thyroid activity or as an index of the intensity of the thyroid intoxication. Rest alone usually caused a marked decrease in the toxicity. Drugs do not materially accelerate this decrease. In some cases the Röntgen-rays produce a definite improvement; in others they are without effect. The usual immediate effect of surgery is a very definite decrease in toxicity, but there is often a subsequent recurrence.

Emaciation.—The marked and rapid emaciation is an almost constant symptom in spite of the large food intake. It was noted by Murray in more than one-third of his 180 cases. This loss of weight varies from fifteen to thirty pounds and may rise nearly to sixty pounds. In a case reported by Mannheim there was a loss of ninety-three pounds in ten months. In very severe cases it may amount to one-third or even half of the original body weight. It usually develops before the diarrhea and vomiting, but is always made worse by these. Huchard has described *"crises of emaciation"* which may be followed by a gain in weight almost as rapid and marked as the loss; thus one patient gained back in ten weeks thirty-three of the sixty-two pounds that had been lost in one year; the gain in weight may take place in spite of the persistence of diarrhea and other symptoms of hyperthyroidism. The emaciation is due to the thyroid intoxication, which in part accounts for its great variation in the different cases.

Fever.—Fever of different degrees of severity and duration was first extensively reported by Bertoye in 1888. In some cases, according to this authority, it may resemble the fever of typhoid and may be associated with other symptoms of fever. Mackenzie (*b*) states that the elevation in temperature does not exceed as a rule one or one and a half degrees Fahrenheit. "I have had observations made in a great number of cases and find that a temperature above 100° F. is quite exceptional." Thompson noted fever above 99° F. in thirty-nine cases, of 101° to 104° F. in fourteen and above 104° F. in seven cases of a hospital

series of forty-three patients. Thompson states that "it is of the septic type, oftenest remittent, but sometimes intermittent and always irregular and occasionally remaining elevated three or four degrees for several consecutive days. The duration of the fever varied from a few days to several weeks. Often it lasted for ten days or a fortnight, in one case for forty days and in another thirty-eight days."

Mackenzie believes that such pyrexia is due to some complication. Even though the temperature be normal, a subjective feeling of heat is the rule, especially at night, and even in cold weather. Further, the patients enjoy cold weather and are very intolerant of hot.

Leopold-Levi in a recent communication on hyperthermia in thyroid disturbances calls attention to the following clinical observations. The subject is always too warm and sometimes suffers from a true "thermophobia." The sensation of heat is localized and is either continuous or intermittent but the temperature is hardly ever above 37° C. The temperature is regularly a few tenths of a degree centigrade above normal or there may exist a mild subfebrile state which is exaggerated by such accessory factors as fatigue, emotion or menstruation. Lastly there may be prolonged fever with remissions.

Protein Metabolism.—The protein metabolism is definitely increased and the nitrogen equilibrium is maintained with difficulty; in the severe cases there is a well defined loss of nitrogen. According to Magnus-Levy (*e*), Lustig was the first to call attention to the increase of nitrogenous metabolism in Graves' disease, but it was Friedrich Mueller who first published convincing data. During the worst periods of the disease a nitrogen-loss is by no means always the rule. In Magnus-Levy's opinion the loss is not due to a relative subelimination but to the "toxic protein disintegration." Janney (*b*) found that the nitrogen balance is a rather delicate measure of the action of the thyroid hormone or Kendall's thyroxin. Janney noted a *gain, not a loss,* of nitrogen as the result of the therapeutic action of the thyroid extract and concluded that loss of nitrogen is due to a toxic action of the gland.

Forschbach noted that only small amounts of creatinin, both endogenous and exogenous, are excreted in the urine in Graves' disease: his observations have not yet been confirmed.

Carbohydrate Metabolism.—This may also be disordered to a greater or less degree. Accordingly we will consider (1) alimentary glycosuria, (2) transitory spontaneous glycosuria, and (3) associated diabetes mellitus.

Alimentary Glycosuria.—In many cases of Graves' disease alimentary glycosuria can be excited by the administration of a carbohydrate-rich meal, or better still of one hundred grams of pure glucose to the fasting patient. Transitory glycosuria, especially of the alimentary type, was noted by Chvostek in 69 per cent of his cases. In marked contrast is

the experience of Naunyn who, in his large series of cases at Strassburg, noted only one case of alimentary glycosuria. Stern, too, noted it only once in a small series of eight cases of exophthalmic goiter. However, Stern admits that alimentary glycosuria occurred in 22 per cent of Mendel's and 36 per cent of Strauss' series. Schulze noted it in 25 per cent of his series, though of a varying degree; he believes it is much less frequent than the adrenalin glycosuria which he found in 80 per cent of his series. Williamson believes that alimentary glycosuria is common and states that it may be induced in some cases by 20 to 30 grams of glucose, while in others 100 grams are required.

Transitory spontaneous glycosuria is not common, though it occurs occasionally in the course of Graves' disease. In Stern's opinion these, with few exceptions, were instances of a diabetic glycosuria considered under the third group. He, however, reports a case of his own and refers to some reported by Chvostek, Kraus and Ludwig. Contrary to the experience of Naunyn, who never saw a case of spontaneous glycosuria in Graves' disease, Williamson states that there is frequently a temporary or intermittent glycosuria, but gives no figures.

Stern further calls attention to the glycosuria produced by thyroid medication in a certain percentage of patients not so far as known subjects of hyperthyroidism; he believes such may occur in those with latent diabetes but also in more or less normal individuals.

Associated Diabetes Mellitus.—A true diabetes seems to occur in Graves' disease somewhat more frequently than does simple glycosuria. The coincidence of these conditions, writes Stern, may be threefold, that is, exophthalmic goiter may arise during the course of diabetes mellitus or it may be contemporaneously produced or the appearance of the diabetic phenomena may be subsequent to that of Graves' disease. Stern found twenty-three such cases in the literature up to the year 1902 and reported two more of his own. Thompson, a few years later, reported three such instances in his series of eighty cases of Graves' disease. Finally, Williamson notes that both exophthalmic goiter and diabetes mellitus may develop after a sudden mental shock or great mental anxiety, and that a family history of diabetes is not uncommon in Graves' disease (which was true in seven of his own series), both of which facts are further evidence of the relationship between Graves' disease and diabetes mellitus.

Hyperglycemia.—Flesch in 1912 noted a complete absence of spontaneous hyperglycemia in Graves' disease, while 60.7 per cent of the same cases showed an "alimentary hyperglycemia" one hour after the ingestion of 100 grams of glucose. Geyelin could not confirm the findings of Flesch and criticizes the latter because he studied only nine *fasting* cases and because of his use of an old, unwieldy method for the determi-

nation of the blood sugar. He believes that spontaneous hyperglycemia is a very common accompaniment of hyperthyroidism—occurring in 90 per cent of the moderate and severe cases studied. In mild cases or during latent periods normal blood-sugar values are commonly obtained. Geyelin also adds that either spontaneous or alimentary glycosuria is an equally constant symptom. Alimentary hyperglycemia (two hours after 100 grams of glucose) and alimentary glycosuria are found not uncommonly in the very mild cases, whereas fasting or postprandial hyperglycemia and spontaneous glycosuria are usually absent. Finally, Geyelin found that, as compared with normal individuals, there is a slower return to the carbohydrate values of the fasting blood after doses of glucose have been given.

Dennis and Aub, because of the conflicting findings of Flesch and Geyelin, made blood sugar studies in eighteen patients with hyperthyroidism and found as did Geyelin alimentary hyperglycemia in every case examined, while fasting hyperglycemia was exceedingly rare. They could find no relation between the degree of hyperglycemia and the intensity of the glycosuria, nor between the severity of the intoxication and the occurrence of hyperglycemia.

Such then is the chaotic state of our knowledge of the carbohydrate metabolism in Graves' disease! But this much is certain, that disturbances of the thyroid do cause disturbances of the carbohydrate mechanism, but whether directly through the thyroid itself or indirectly through the pancreas is another question.

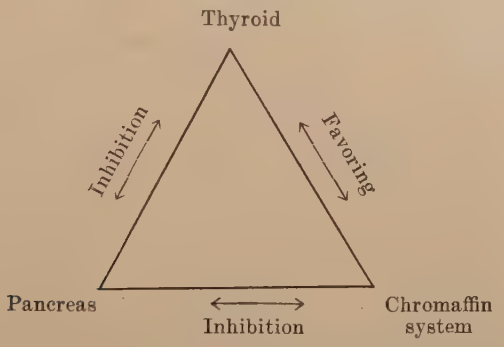
Fat Metabolism.—This is said also to be occasionally affected, though certainly less frequently and to a less degree than the protein or even the carbohydrate metabolism. Under the gastro-intestinal section we have already referred to a disturbance of fat absorption, resulting in fatty diarrhea. In the same section mention is also made of cases of steatorrhea from an absence or great diminution of the fat splitting ferment from an associated pancreatic disease. We know of no routine, careful investigation of the fat metabolism in any series of cases of uncomplicated Graves' disease.

Mineral Metabolism.—There is often a *phosphorus loss* especially through the feces, according to W. Scholz. Falta states that this is related to a *calcium loss* through the intestines. Clemens found also a chlorid loss in the urine in conjunction with the polyuria.

Kummer from a very careful study of one case of exophthalmic goiter found a negative mineral balance during the eleven days' observation; the patient lost large amounts of phosphorus and calcium as well as a little magnesium. He concludes that the emaciation in exophthalmic goiter is not only caused by loss of fats but also by a loss of minerals. Kummer further concludes that it is not only a question of malassimilation but also of absorption of the ingested mineral material.

Associated Endocrinopathies

"While the interrelation of the various endocrin glands has recently been the object of serious investigation, particularly by the younger Vienna clinicians (Falta, Eppinger, Ruedinger and von Noorden, Jr.), "it must be confessed that the theories as yet almost outnumber the facts," writes Barker. Inasmuch as objective measurements could most readily be applied to changes in metabolism, it was to these processes that most of their experiments were directed, in an endeavor to ascertain how far a given hormone acts on the visceral nervous system and how far indirectly through other endocrin glands. Their results and theories are summarized in the accompanying diagram, which appears in their paper of 1908.



From this it will be seen that the pancreas and thyroid on the one hand, the pancreas and the chromaphil system on the other hand, mutually inhibit one another's activities. Again the thyroid and the chromaphil system reciprocally favor each other's activities—a hypofunction or a hyperfunction of the one gland leading to a hypo- or hyper-function of the other. Hence hyperthyroidism must lead to an insufficiency of the pancreas and to an increased activity of the suprarenals, while hypothyroidism must lead to overfunction of the pancreas and a diminution of adrenal activity. The Vienna school think that the glycosuria of hyperthyroidism is an indirect effect through the chromaphil system and that the hyperexcitability of the sympathetic nervous system as shown by the epinephrin-mydriasis test, is to be similarly explained.

The *sympathicotonic* cases of Graves' disease with the protrusio bulbi, negative von Graefe, positive Loewi, and positive Moebius' signs, dry eyeballs, marked tachycardia, dry skin, constipation, alopecia, slight fever, eosinophilia and alimentary glycosuria, they attribute to thyrogenic hyperactivity of the chromaphil system.

To explain the *vagotonic* cases, with the relatively slight tachycardia, the marked subjective feelings of palpitation, positive von Graefe's sign, wide lid-slits, negative Moebius' sign, slight or absent protrusio bulbi,

lacrimation, sweats, diarrhea, gastric hyperacidity, eosinophilia, lymphocytosis, pulsus irregularis respiratorius and normal or increased carbohydrate tolerance, they assume the existence in the thyroid excretion of a compound that in its pharmacological action resembles the vagotropic drugs pilocarpin and muscarin, and that has an especial affinity for the craniosacral autonomic nervous system and which can be neutralized, in part at least, by an antagonistic vagotropic drug—namely atropin.

Their findings and theories received the approval of Barker and Sladen. Meltzer and many other physiologists are opposed to such speculations and especially to the use of diagrams, from the fear that those unfamiliar with the subject will take hypotheses for facts. Nevertheless we cannot but feel that just as Ehrlich's side-chain theory of immunity and its bizarre diagrams have helped to stimulate investigation of many of the abstruse problems of infection, so will the theories and diagrams of the Vienna School aid in the investigations of the equally obscure field of endocrinology. We further agree with Barker that an analysis in every case of Graves' disease of the symptoms with reference to the functions of the pancreas, the suprarenals, the gonads, the thymus, the hypophysis and the chromaphil system, is always instructive and may often lead to the discovery of anomalies and relationships that might otherwise be entirely overlooked.

Thymus Disorders.—Markham, in 1858, was the first to call attention to the thymus hyperplasia of exophthalmic goiter; since then it has been confirmed by many other observers. While Matti believes the frequency of thymic hyperplasia has been exaggerated, he found it in 76 per cent of all fatal cases of exophthalmic goiter, but especially in those dying following the operation of thyroidectomy. He believes there is no experimental evidence that the pathological changes in the thymus and thyroid are the results of correlative reactions. Capelle and Bayer found that 95 per cent of all autopsies on subjects of Graves' disease dying from the immediate effects of the malady or the operation showed some hyperplasia. Mackenzie (*c*) reports that at twenty-six necropsies in which the condition of the thymus was noted it was described as greatly enlarged in six, large or hypertrophied in sixteen and persistent but not large in four: i. e., a definite hyperplasia was found in 77 per cent. It was noted that in some cases, although the gland was enlarged, it showed the histological changes of degeneration or some degree of fibrosis. In Blackford and Freligh's series of thirty-seven patients under forty years of age that came to autopsy, the thymus was found hypertrophied in all, while it was absent in nineteen of thirty-six patients who died of Graves' disease after the age of forty; in other words, a hypertrophic thymus was present in 73 per cent of seventy.four carefully studied cases.

In some cases even a thymectomy without a thyroidectomy may be followed by a marked subjective and objective improvement. The Graves'

disease thymus has shown marked hyperplasia of the medulla of the gland, the presence of many Hassall's corpuscles and accumulations of eosinophils along the septa of the gland and about the blood vessels. Capelle and Bayer believe that both the thyroid and thymus produce an internal secretion that there are two components, one sympathicotropic and one vagotropic. They believe that variations in the proliferation in both the thyroid and thymus will account for the manifold types of Graves' disease that one meets with clinically. The thyroid influence is, on the whole, predominantly sympathicotropic in contrast to the thymic effect which is predominantly vagotropic. Indeed, some observers believe in the possibility of Graves' disease being due primarily to disease of the thymus. It is maintained that thyroid intoxication leads to hyperplasia of the thymus and thymus intoxication to enlargement of the thyroid. We are inclined to accept the conservative view of Mackenzie, who writes: "What part the persistence of the thymus gland plays in the disease is at present uncertain. The possible relationship of the exophthalmic goiter to the condition known as lymphatism or status lymphaticus has to be considered . . . It is significant that a persistent thymus is found in so large a proportion of the cases of exophthalmic goiter which succumb under operation."

According to Launoy, Bircher has claimed to have experimentally reproduced in dogs Graves' disease by an intraperitoneal implantation of portions of the thymus gland removed from non-goitrous persons dying under an anesthetic. Against such claims Launoy points out that the success of thymectomy in exophthalmic goiter has not been demonstrated, nor does experimental removal of the thymus result in atrophy of the thyroid. According to Eppinger, Falta and Hess, as well as Capelle and Bayer, the particular symptoms which indicate a preponderate influence of the thymus gland in Graves' disease are the vagotonic. Halsted (*c*) (*e*) rather questions this last statement in his interesting paper on the significance of the thymus in Graves' disease. Klose believes that in Graves' disease the thyroid is qualitatively and not merely quantitatively altered and may cause toxic as well as mechanical injury to the heart; Matti, however, states that there is no relationship between the thymus and cardiac hypertrophy. Further, Klose and Borchhardt attribute the lymphocytosis of Graves' disease to the thymus, but in this they have not the complete support of Halsted. We believe we cannot do better in closing this discussion than to quote directly from Halsted: "From the facts gleaned at the autopsy table, from experiments on animals and, above all, from the result following primary thymectomies we have convincing evidence that the thymus gland may play an important part in Graves' disease and in some cases assume the title rôle. Some of the most puzzling features of the disease are made possible of interpretation by the discovery of the influence which the thymus may exert."

Parathyroid Disorders.—The observations of Vincent and Jolly reveal the morphological and functional relationships between the parathyroid and thyroid glands and that "when the thyroid is removed the parathyroids appear capable of functionally replacing it to a certain extent and their histological structure changes accordingly." [4] However true this may be of the experimental normal glands, Humphry examined the parathyroid glands from four cases of Graves' disease and noted no signs of compensatory hypertrophy or any evidence of the gland cells' becoming more specialized and forming colloid. He found, on the other hand, an extensive fat infiltration in three of the four cases; further, microscopically in one case at least, the cell protoplasm was diminished while the cell nuclei were large and crowded together. Humphry admits that some degree of fatty infiltration of the gland may occur normally. The investigations of W. G. MacCallum have proven that the part played by the parathyroid glands is neither important nor specific. While we have seen only one case of tetany complicating Graves' disease there are numerous references to such in the literature (Steinlechner's for example) and tetany of course was formerly not uncommon following strumectomy when some injury has been inflicted on the parathyroid glands or their blood supply.

Gonads, Disorders in Function of.—Cheadle long ago called attention to the atrophic changes of the genitalia in exophthalmic goiter. No appreciable anatomical change has been noted in the male sex glands, though, as previously stated, loss of libido and potentia is not uncommon.

According to Elmer "the behavior of the thyroid during puberty, menstruation, pregnancy, labor and lactation argues in favor of its close relation to the uterus and its dependencies." He quotes Freund's statement that without exception there was a chronic atrophic parametritis in all his cases of exophthalmic goiter. Dysmenorrhea and amenorrhea are quite common, but scarcely more frequent than in other systemic diseases. Repeated pregnancies are by no means rare during the course of the disease. Atrophy of the uterus has been very occasionally reported. Elmer believes that there is an unusual frequency of uterine neoplasms with thyroid abnormalities, more particularly with various forms of typical and atypical exophthalmic goiter. He has not been able to confirm the teaching of some that surgical removal of one will benefit the progress of growth in the other.

The loss of the pubic and axillary hair has been assigned by some to atrophy of the sexual apparatus. The breasts usually atrophy with the general emaciation but occasionally the atrophy is unilateral; here again, alterations in the sexual activity may play a rôle. In Basedow's male case there was unilateral distention of the veins.

[4] Vincent has recently expressed a doubt of the validity of his former views on this subject.—R. G. H.

Hypophysis Cerebri, Disorders in Function of.—Acromegaly may complicate Graves' disease according to both Ballet and Holmgren (*a*). Walsh (*b*) has also recently reported a case of atypical acromegaly in a woman with exophthalmic goiter associated with a congenitally high forehead. From the history it would seem that the acromegaly antedated the hyperthyroidism by many years as the former was present for some years before the sudden development of the latter, after a severe mental shock.

MacCallum (*b*) found no evidence of disease in the one case in which he investigated the hypophysis.

Hofstaetter in an excellent paper points out that some of the symptoms of exophthalmic goiter can be better explained by an injury of the hypophysis than by a hyperfunction of the thyroid gland: for example, the fever, the polyuria, polydypsia, some of the trophic disturbances, the fat deposition, the insomnia and the occasional increase in growth. Further, he believes that the phenomena which are usually assigned to an increased epinephrin output can be explained by the hypophyseal influence. The results of hypophyseal therapy all speak for a hypofunction of the gland in exophthalmic goiter. The belief of Salmon that the hypophysis plays the chief rôle in the etiology of exophthalmic goiter does not seem tenable to Hofstaetter, for the hypophyseal are not the chief symptoms, nor does hypophyseal therapy benefit the cardinal symptoms. Animal experiments suggest that part of the benefit when hypophyseal extract is given therapeutically to man is to be referred to the associated hyperepinephrinism. He believes that the hypophyseal pathology is not the cause but one of the very early results of the dysthyroidism.

Suprarenal Disorders.—There seems to be little doubt that many of the symptoms of Graves' disease can be assigned to an affection of the adrenal glands, namely, the pigmentation, weakness, diarrhea and the positive Loewi phenomenon. Further, some cases of co-existence of Graves' disease and Addison's disease have been reported by Eulenburg and Oppenheim. The latter's case, in addition to pigmentation of the skin, had a pigmentation of the bulbar conjunctivæ and mucous membranes of the lips, as well as a marked asthenia. Fraenkel has shown that the blood of three well marked cases of Graves' disease contained four to eight times the amount of adrenalin that the normal controls revealed and that, in spite of an absence of evidence of hypertonus. The actual figures were 50 to 100 milligrams in the total blood stream of the exophthalmic goiter cases as compared with the normal 12.5 milligrams. It would suggest that the function of the adrenals may be both stimulated and depressed in different stages of the disease.

Simmonds (*a*) as well as Hedinger have noted hypoplasia of the chromaphil system in cases of exophthalmic goiter and status thymolymphaticus.

Matti found that the suprarenals in one of his cases were smaller

than normal while there was a definite atrophy of the medulla; in a second case there was almost complete atrophy of the medulla of both adrenals. He is inclined to emphasize the importance of the chromaphil system in certain combination cases both from clinical observation and from experimental investigation. Further, he believes that the hypertrophy of the suprarenal medulla results from the loss of the theoretical thymic function.

Pancreas, Disorders in Function of.—Cohn and Peiser have called attention to the presence in five cases of disease of the pancreas (three hemorrhagic, one suppurative and one chronic interstitial pancreatitis) of the ocular symptoms which are commonly associated with hyperthyroidism: thus they found slight exophthalmos in four, a positive von Graefe sign in four, positive Moebius and Stellwag signs, tremor, dermatographia and tenderness of the thyroid gland in five, while a lymphocytosis of from 22 to 40 per cent was present in four cases. Their observations have been confirmed in one case by Garrod (*b*), who writes that "where thyroidal and pancreatic symptoms are seen in association, the thyroid appears to be the organ primarily at fault and the observations of Cohn and Peiser, for which the converse holds good, are of all the greater interest on that account." If, in pancreatitis, the eye symptoms are due to an excessive thyroid secretion, it is really the sympathetic nervous system which is stimulating the gland to overactivity and it is not wonderful that the sympathetic should be disturbed when the pancreas is the seat of the disease, when one considers how near a neighbor it is of the great abdominal ganglia and plexuses.

Neuromuscular Symptoms

Cerebral Symptoms.—A change in the *mental condition* of the patient is often one of the earliest symptoms of exophthalmic goiter, although occasionally one meets with a case in which the patient remains placid, good tempered and amiable throughout the course of the disease. Mental irritability, excitability and restlessness are among the early manifestations. The subjects long for continual changes and must constantly be seeing or doing something new. At times the patient is low spirited and tearful; at others cheerful and smiling but always resents being thwarted or contradicted. Apprehension and anxiety are especially common.

There is often *insomnia,* or at least the sleep is disturbed and restless because of disagreeable dreams, from which the patient awakes in a fright. Sometimes somnambulism occurs.

The *moral nature* may be so perverted that the patient becomes spiteful, untruthful, suspicious and generally discontented. The *intellectual powers* may remain unimpaired, but various phobias and obsessions are also

frequently noted. Some patients have a morbid exaltation with a capacity for great mental labor. This mental condition is aptly described by the term "chorea of ideas." In many cases these early symptoms are diagnosed as either neurasthenia or psychasthenia, and the underlying hyperthyroidism is overlooked. It is a good rule to consider in every case of neurasthenia or mild psychosis the possibility of an underlying hyperthyroidism.

Raymond and Serieux state that the psychic symptoms are not an integral part of the disease but develop because of some hereditary psychopathic taint, which is stimulated by the same cause as has produced the exophthalmic goiter. They point out that any form of *mental disease* can occur either preceding the onset of the Graves' disease syndrome, during its course or even after its apparent cure. We are more in agreement with Parhon, Matéesco and Tupa, who consider that the psychic functions are influenced and regulated in a large measure by the activity of the thyroid gland. We would, therefore, suggest that the mental excitement and unrest at least,—possibly even the actual psychosis,—may be due directly to the hyperthyroidism.

In any event Murray noted the development of a true insanity in three patients in his series of 180 cases. Again Kappenburg reports that eleven of the fifty-six cases of "parenchymatous goiter" seen in the general hospital at Utrecht showed either manic-depressive insanity or melancholia. Martin and Shenk (quoted by Murray (*b*)) collected from the literature forty-four cases of definite exophthalmic goiter complicated by mental disease which was classified as mania in sixteen, melancholia in ten, delusions of persecution in ten and various other psychopathies in the remaining eight. Woodburn believes that only a relatively small proportion of hyperthyroid cases actually become insane. He concludes from a study of four hundred and sixty such cases that there is no distinct thyrotoxic psychosis but that certain well defined neurotic and psychic symptoms may arise in well marked thyrotoxic cases. In the exophthalmic goiter patient the symptoms are of the overcerebration and overstimulation type dependent upon (a) cerebral hyperemia, (b) the thyrotoxicosis per se and (c) a toxicity from the increased waste products of metabolism.

In conclusion we would insist that while recovery from such a psychosis is possible, the prognosis is very grave.

Sensory Symptoms, General.—Barker emphasizes the rarity of phenomena referable to the peripheral neurones (both sensory and motor) of the cerebrospinal nervous system; this in marked contrast to the manifold symptoms due to disturbances of the sympathetic and parasympathetic systems. Among the sensory phenomena, subjective symptoms are common and these are not confined to the ordinary sensibility for the special senses are also involved; thus subjective luminous phenomena and subjective auditory symptoms have been described. There are also paresthesiæ in

the extremities as numbness, tingling and formication. Hyperesthesia is as usual in the sensory tracts as is tremor in the motor nervous mechanism. Thomson has called attention to the frequency of tenderness of the auricle of one or both ears. Pains in the tips of fingers and toes and in the heels are common. Local twitchings and cramps, especially in the legs, may be troublesome at night. As a rule these cramps do not last long but occasionally Mackenzie has observed more persistent spasm in which the hands assume the more characteristic form seen in tetany.

Headache does not seem to be common in the experience of most clinicians, yet Swan (*a*) noted it in thirty-one of his series of fifty cases; it was either general in distribution or localized to the frontal, occipital or vertical regions. Neuralgias in various parts of the body are by no means rare; thus a facial neuralgia is sometimes a troublesome and obstinate symptom. Vertigo and globus hystericus occur in the less severe cases. Dock reports a temporary paraphasia in one case.

Special Senses.—Among the *ocular symptoms* one must mention pain in the eyes, amblyopia, diplopia, achromatopsia, narrowing of the visual fields, scotoma, and transient blindness. These usually affect only one eye. Paralysis of the ocular muscles will be discussed under complications. A *pulsation of the retinal vessels* was first noted by Becker in 1857, according to Sattler, and has been confirmed by many since then. *Nystagmoid movements* have been noted by Moutet, Sainton et Pisante, Levi et Rothschild, and more recently by Sainton. Indeed, according to the latter author they were present in twenty-two out of the forty cases in which they were sought for; he admits that they were spontaneous in only two cases, while in the other twenty cases they were elicited only in the extreme lateral position of the eyes. In these cases the nystagmus was in a more or less rapid horizontal or oblique axis. Three cases of *rotatory* nystagmus have been reported. Two of these which were reported by Bramwell and Snell (quoted by Sattler) occurred in coal miners in association with Graves' disease, but must be discounted because of the well known association of nystagmus with coal mining. However, Frankau has described a third case of bilateral rotatory nystagmus in a tradesman afflicted with exophthalmic goiter but with normal vision and eye grounds.

Among the *auditory symptoms* are a sense of fullness or throbbing in the ears, transient but sometimes persistent deafness, tinnitus and severe aural vertigo.

Anosmia occasionally occurs.

Motor Symptoms.—*Tremor* is so characteristic of exophthalmic goiter that since the days of Charcot it has been classed as one of the cardinal symptoms. As to whether the tremor is to be regarded as a motor nervous manifestation or a muscular one is still uncertain; we prefer to consider it the former. It affects the flexor and extensor muscles of the wrists and not the intrinsic muscles of the hand so that the fingers

do not vibrate independently but the hand moves as a whole. It was observed by Murray to be unilateral when the goiter and exophthalmos were also confined to one side. A large percentage of the cases, though by no means all, present a tremor. Thus Murray noted it in one hundred and eleven of his first series of one hundred and twenty patients or in 92.5 per cent. It is fine or of small amplitude and rapid with seven to ten oscillations per second; it is especially troublesome to the patient when performing such movements as sewing or drawing a straight line. It is best induced in the fingers when the arm is held out rigidly with the fingers wide apart. It can often be brought out by placing a thin card or a heavy piece of writing paper upon the upturned fingers. The tremor affects the whole extremity and not the fingers only; it may be observed in the leg as well as in the arm and is sometimes present in the toes. In some cases, as we have said, it is limited to, or more intense in, one limb. Attacks of trembling may affect the whole body and, according to Mackenzie, "such attacks bear the same relation to the tremor that palpitation does to the rapid cardiac action." The tremor was first recorded by Pierre Marie (*b*) (1883), who found a characteristic tracing in exophthalmic goiter. Peterson also made very careful kymographic tracings of the tremor and found that the individual vibrations numbered 8.7 to 12 per second in Graves' disease, 8.5 to 12 per second in chronic alcoholism, 5.4 in multiple sclerosis and 3.7 to 5.6 per second in paralysis agitans. The earlier measurements of Marie (5 per second), Charcot (4.5 per second), and Graves (4.8 to 7 per second), were by a sphygmograph—an instrument not as suitable for the estimation of tremor as was the kymograph used by Peterson.

Muscular Weakness.—This is another very characteristic symptom and is well brought out clinically by the difficulty in climbing stairs from an involvement of the quadriceps extensor muscles and in the hurried and shallow breathing from an alteration in the intercostal muscles and diaphragm. According to Balfour "the weakness is often most striking in the ham-string group of muscles and the patient's difficulty or inability to step onto the foot-rest of an examining table is very characteristic." Wilson (*d*) believes it is probable also that one of the large factors in the production of exophthalmos itself is the weakness and relaxation of the recti oculorum. The weakness may be associated with muscular atrophy and degeneration according to Askanazy, who states that the muscles most affected are those of the thorax, abdomen, pelvis, eyes and tongue. Mueller gave some careful measurements of the degree of weakness estimated in kilograms; he found, for example, that the power of flexion in the right finger of a normal woman was twenty whereas that in a case of Graves' disease was only six and one-half kilograms. The various muscle groups of the shoulders, elbows, hips and knee joints showed the same marked discrepancy. Charcot (*b*) has noted a rare sign in "para-

paresis," or the sudden giving way of the legs like that seen in intermittent claudication. It was noted by Mackenzie in twelve cases and considered by him as functional in origin though without other symptoms of hysteria. On the other hand, weakness of the legs in climbing stairs or even in walking is quite frequent. It may go on to a paraplegia with loss of skin and patellar reflexes, but, of course, without bladder symptoms, loss of sensation or marked atrophy. The myasthenia may be cerebral in origin or possibly like myasthenia gravis be associated with the thymus hyperplasia, which, as has already been stated, is so common in Graves' disease.

Muscle Atrophy.—Ballet was the first to note the atrophy of the muscles of the legs in a case of exophthalmic goiter. Miesowicz examined nine hundred articles in the literature on exophthalmic goiter and found only fourteen cases reported, including his own case. In the latter there was an extensive muscular atrophy of the upper extremities associated with a severe form of Graves' disease. In a case reported by Silva the atrophy was especially noticeable in the muscles of the hand. Askanazy noted in his four cases a marked and widespread fatty infiltration and fatty degeneration of the voluntary muscles, characterized macroscopically by the small size and pallor of the muscle bundles and microscopically by nuclear changes and fatty degeneration of the protoplasm. Askanazy considered these changes a result of the toxic action of the thyroid secretion on the muscle bundle itself. Miesowicz believes that such cases, exceptional though they be, point to a central origin.

Other Motor Manifestations.—The tendon reflexes are usually slightly exaggerated and true spastic phenomena have been reported. *Monoplegia* and *hemiplegia* have been described. Choreiform movements also occur occasionally. *Tetany, epileptiform convulsions, ascending paralysis,* and *multiple neuritis* are also reported but are probably best considered as complications and not as symptoms of the disease.

Symptoms in the Hematopoietic System

The Blood.—*Hemoglobin and Red Cells.*—The older writers were in the habit of emphasizing the presence of an anemia as part of the clinical syndrome. Indeed, Begbie thought it was primary and wrote on "Anemia and Its Consequences—Enlargement of the Thyroid Gland and Eyeballs," whilst Wilks cautioned the inexperienced clinician to beware of mistaking Graves' disease for ordinary anemia. This erroneous belief can only be explained by the frequent existence of pallor in the patient, which, in the absence of a blood count, was thought to be a symptom of anemia. For many years it was stated in text books and magazine articles that a chlorotic anemia is present in the disease. Neither Albert

nor Theodore Kocher (*g*) was able to find any tendency to chlorosis in their cases. Plummer (*e*) found from a study of 578 cases of Graves' disease that the percentage of hemoglobin averaged 83.1 and the number of red cells 4,790,000 per cubic millimeter—figures within the normal limits or at least not to be considered indicative of a chlorosis. No doubt a mild secondary anemia may occasionally occur.

Leukocytes.—There is a general impression that there is a leukopenia in exophthalmic goiter. However this is not the rule, as Plummer's average leukocyte count for his 578 cases, 6,973.5 per cu. mm., shows; this is a low but normal figure. According to Naegelsbach it was Cuiffini who, in 1906, was the first to note a peculiar leukocytic formula in hyperthyroidism. This has received ample confirmation by many clinicians. There is first a relative or even an absolute increase in the lymphocytes which sometimes amount to from 35 to 60 per cent of the white cells. The large mononuclear cells may also be increased and form 6 to 8 per cent. There is a corresponding neutrophilic leukopenia, sometimes, according to Albert Kocher, to such an extent that the polynuclear neutrophils may be actually fewer than the lymphocytes and large mononuclears. While usually the eosinophils are diminished in number, there is occasionally an eosinophilia, an evidence, according to Eppinger and Hess (*b*), of irritation of the parasympathetic nerves. In rare cases two to three per cent of myelocytes have been noted. Reckzeh suggests from his experimental work in dogs that the relative lymphocytosis and leucopenia indicate a bone-marrow injury resembling that in the toxic experimental anemia. Salis and Vogel found that a short course of iodin-therapy in typical cases of Graves' disease caused a disappearance of this lymphocytosis, while a prolonged course of the same drug caused a return of the lymphocytosis to a point higher than formerly. The exact significance of this observation is questionable, to say the least. Plummer believes that this change in the leukocytic formula is due to two more or less independent variables, one which causes the lymphocytosis, namely the hyperplasia of the lymphoid tissues; the other which influences the neutrophils—a fluctuating abnormal distribution of the polynuclear neutrophils in the vascular tree. Barker (*b*) states that recent studies point to the status thymico-lymphaticus as responsible for the lymphocytosis. Klose maintains that the thyroid intoxication leads to a hypogenitalismus which, in turn, causes the status thymico-lymphaticus with its lymphocytosis. Albert Kocher insists that the lymphocytic increase is proportional to the severity of the disease, but that it is sometimes absent in severe cases, when the prognosis is serious; in the stage of improvement the differential picture returns to nearer normal. In Plummer's opinion, however, there is nothing to show that the degree of lymphocytosis is correlated in any way with the duration of the symptoms of Graves' disease. Naegelsbach further admits that the degree of lymphocytosis

does not indicate the severity of the disease; he, however, noted that strumectomy resulted in a diminution of the lymphocytosis as well as an improvement in the other symptoms. Finally it is believed by careful students of the endocrin glands that the relative mononucleosis is not distinctive of hyperthyroidism but is common to all forms of hyperactivity of the internal secretions.

Viscosity.—The viscosity of the blood is usually lowered so that the coagulation time is delayed according to Fr. Mueller and the Kochers. Further, Crotti as well as others found that the blood shows a diminished coagulability in Graves' disease in contrast to the materially increased coagulability in myxedema. This is due, according to Kottmann (quoted by Crotti), to the increase of the antithrombin content of the blood. Kocher believes that this contrast in the coagulation time of hyperthyroidism and hypothyroidism serves as an excellent differential diagnostic symptom in doubtful cases.

Hemorrhages.—Occasionally according to von Leube there is a pronounced inclination to hemorrhage from the various mucous surfaces in the form of epistaxis, hematemesis, hemoptysis, and melena. Purpura has been mentioned under the cutaneous manifestations.

Lymphatic Glands.—The lymphatic glands of the neck are always found enlarged at the operation on exophthalmic goiter. In many cases the cervical glands are palpable clinically as was first noted by Gowers; they are not as a rule tender. In a small proportion of cases the axillary and inguinal glands are also enlarged, and in very rare cases all the superficial glands have been perceptibly increased in size.

The Spleen.—Stewart and Gibson have reported the occasional enlargement of the spleen in exophthalmic goiter, though sometimes, as in one of their own cases, there was a history of previous attacks of malaria. A palpable spleen, however, is not difficult to explain as a part of the general lymphoid hyperplasia that is so frequent in this syndrome.

The Thymus is rarely found clinically enlarged in spite of the frequency of post-mortem findings, which have been discussed by us elsewhere. Nevertheless Beebe (*b*) states that he found a clinical enlargement of the thymus gland in 35 per cent of his cases. Careful percussion of the retrosternal region and a skiagram should be made in every case.

Complications

Some of these have already been considered under the symptomatology as unusual symptoms of exophthalmic goiter rather than complications. As far as possible repetition will be avoided.

In Endocrin Glands.—Myxedema is more usually a sequel and not a complication; however, sometimes the symptoms of the two diseases run

synchronously in the same patient. In such an event surely the term "Dysthyroidism" seems justified.

The other diseases of the ductless glands as diabetes mellitus, acromegaly, and Addison's disease, have been discussed.

In Locomotor System.—Sattler collected from the literature in 1880 thirteen cases of exophthalmic goiter associated with *osteomalacia.* Some years later Koeppen made a post-mortem diagnosis of osteomalacia in a patient with Graves' disease associated with kyphoscoliosis; he saw another patient with kyphoscoliosis and dental caries. It was not until 1919 that another case was added by Hitzenberger, who suggests a possible etiological relation between the two conditions and that osteomalacia may be due to an internal secretory dyscrasia. We agree with the suggestion of Hofstaetter that the complication may be assigned to the hypophysis.

Revilliod speaks of the pointed fingers as well as of the exaggerated flexibility of the interphalangeal joints in patients with Graves' disease. Holmgren (*a*) noted that in eighty-nine cases of Graves' disease occurring before the fourteenth year there was an unusual growth in the long bones with early ossification; he emphasizes the contrast of this increased growth in young exophthalmic goiter patients with the dwarfism of cretinism and assigns it to a hyperfunction of the thyroid gland. In a later paper he reported one hundred and twenty-seven cases of hyperthyroidism in youthful patients with an increase in length of body in seventy-five per cent.

Trophic Changes.—*Decubitus ulcers* have been reported in rare cases according to Moebius.

Arthropathologic Conditions.—*Chronic arthritis* and *intermittent hydrarthrosis* are occasional complications.

Angiosclerotic Changes.—Gangrene of one or both legs has been reported according to Moebius (*b*). This is probably senile in origin and merely hastened by the coexisting Graves' disease.

Hematopoietic System.—Chlorosis is sometimes observed in the young female suffering from Graves' disease or in a case running a very acute course.

Pernicious anemia and Graves' disease have been reported occurring in the same patient by Neusser (quoted by Dock (*b*)); in this case atrophy of the liver was found post mortem. Jaccoud reported another case with icterus, purpura and fatty degeneration of the liver. In the case reported by Stockton and Woehnert there was a thrombosis of the superior vena cava and innominate veins, which developed in the course of acute Graves' disease complicated by cardiac insufficiency.

Nervous System.—Complete paraplegia and hemiplegia of an organic nature have been observed in a few cases.

Hysteria occurs in 25 to 34 per cent of cases in Murray's experience, and is manifested by alteration in sensation, paresis, paralysis, convul-

sions, astasia-abasia and contraction of the fields of vision. Many of the cases of so-called epilepsy are rather examples of major hysteria or hystero-epilepsy.

Epilepsy may occur as a coincident disease or as a complication. In the latter case Ballet suggests that it is due to changes in the cerebral circulation dependent upon the damaged action of the heart.

Paralysis agitans has been found as a rare association of Graves' disease, according to Moebius and Gordon (quoted by Dock).

Tetany.—"Idiopathic tetany" seems to be a very rare complication though it has been mentioned in the literature. In one case in our own series typical tetany seizures were observed on several occasions in a young woman with a moderately severe form of Graves' disease; while no Trousseau phenomenon could be elicited there was a distinct increase in the mechanical and electrical irritability of the nerves.

"Post-operative tetany" must have been relatively common in the early development of the surgical treatment of the disease. Judd, of the Mayo Clinic, has observed only seven or eight instances of temporary tetany, apparently resulting from trauma to the parathyroids during therapeutic strumectomy; in one instance it followed the ligation of both inferior thyroid vessels at one operation and was the most severe case. While it persisted for seven weeks it was controlled by calcium lactate.

Tabes dorsalis is often a complication, in Dock's opinion; though we must confess never to have seen it ourselves, there is not infrequent reference to it in the medical literature, especially of France. It is of interest because its presence would suggest the possibility of the syphilitic origin of the thyropathy in such a case.

Thomsen's disease has also been reported as a complication.

Cerebral Nerve Paralyses.—Sattler and Kappis have collected all the cases from the literature up to the year 1911. Heuer, five years later, was able to find eighty cases and added one of his own. It is probably a rare complication in spite of the number in the literature, as on account of its rarity the majority have no doubt been reported. A review of the literature shows that almost every cerebral nerve has been involved either alone or in combination with other nerves. The most interesting is a group with the picture of "bulbar paralysis" as seen in Heuer's case and in ten others in the literature. The spinal accessory appears to be the only cranial nerve to have escaped involvement in exophthalmic goiter; thus Heuer found isolated palsies of the first, second, third, fourth, sixth, seventh and ninth nerves quite commonly and combined lesions of the motor fifth, eighth, tenth and twelfth nerves in the bulbar cases not infrequently. The third or oculomotor nerve has been the most frequently involved and next to it the sixth or abducens. Ballet concluded from a consideration of his five cases that the ocular palsies may occur alone or in conjunction with other phenomena of hysteria and regards them as of

bulbar origin, though not necessarily from organic disease. Heuer, on the other hand, assigns the cerebral nerve palsies to the toxic effect of the hyperthyroidism upon the nuclei of the nerves.

Tuberculosis.—This has already been discussed under "etiology." Lévy and others have noted the frequency of hyperthyroidism in the tuberculous patient; Lévy reports thirteen cases of frank exophthalmic goiter and fourteen cases of definite hyperthyroidism among one hundred and seventy patients with tuberculosis. As has been said, there is a divergency of opinion as to the frequency of the association of the two diseases; thus Greenfield found tuberculosis often as a complication of myxedema but never in exophthalmic goiter.

Clinical Types of Exophthalmic Goiter

There are many and various classifications of the clinical types of exophthalmic goiter, but all have their faults and limitations.

Primary cases are those in which the goiter develops coincident with or shortly after some other cardinal symptom of the disease.

Secondary cases are those in which the symptoms of hyperthyroidism occur in the subject of a previous goiter. It must be confessed that in the so-called primary cases a goiter has often existed prior to the symptoms without the knowledge of either patient or even his physician, which greater care in the physical examination might have revealed. Surgeons are frequently struck with the frequency with which operation reveals a distinct enlargement of the gland, which could only have been recognized preoperatively by the discovery of a thrill or murmur over the gland.

According to Kocher's (*d*) well known classification there are three distinct types: (1) *The struma vasculosa* or vascular goiter which occurs in the early stage of exophthalmic goiter, when the symptoms are mainly local. (2) *Struma basedowificata,* or Basedowized goiter, is a milder form of hyperthyroidism developing in a patient with a preëxisting simple goiter. (3) *Struma basedowiana,* or Basedowian goiter, which is the typical form of the disease.

Again, the *duration* of the symptoms may form the basis of the classification, when one speaks of the peracute or fulminant, the acute and the chronic forms. The *peracute* cases are those in which the symptoms come on in a few hours and develop rapidly, and in which the course is short and stormy and the issue is usually fatal.

The *acute* type is distinguished from the chronic by the duration of the symptoms—which in the former may be present for a few weeks or months or even a full year, according to some writers. Many of the acute cases in the opinion of Arneill, if the history had been more critically obtained and the physical examination more carefully performed, would

have shown distinct signs of the disease months or years before the sudden appearance of the more striking symptoms of struma and exophthalmos. In these acute cases circulatory symptoms of tachycardia, irregularity of the pulse and the dyspnea are usually marked; in addition, vomiting, diarrhea, fever, sweating, pigmentation and vasomotor cutaneous disturbances are frequent.

The *chronic* type includes the vast majority of cases of exophthalmic goiter. In this group after months or years of vague neurasthenic symptoms the cardinal clinical features gradually make their appearance and persist for years, sometimes throughout the lifetime of the patient, in spite of all remedial measures.

According to the *number* of the symptoms, cases are spoken of as complete, incomplete, abortive, rudimentary or larval.

In the *complete* or typical cases the four cardinal symptoms of tachycardia, struma, protrusio bulborum and tremor are present.

In the *incomplete* forms only one or two of the main symptoms are manifest. However, as Dock (*b*) points out, "in a disease with so many symptoms the question of completeness must depend largely upon the accuracy of the observations and the care in noting them." Some further qualifying term would be of assistance in such cases, since without it we do not know whether the "incomplete case" lacks exophthalmos or goiter or even whether it has none of the classical symptoms except tachycardia, emaciation and nervousness. To such cases we are in the habit of applying the term "simple hyperthyroidism."

In the *abortive* cases the onset is usually abrupt but is soon followed by a rapid improvement; in the great majority of these, however, as in the acute cases, a careful inquiry will reveal a long history of some slight symptoms. Some mental shock, physical exertion or infection will light up the latent stage into a more or less complete syndrome. This acute stage will then be followed by a period of relative improvement. So true is this to a greater or lesser degree of the majority of cases that Renaut has suggested the recognition of a latent stage, a stage of tolerance and a stage of intolerance. Exacerbations tend to develop rapidly but to subside gradually and to recur at longer or shorter intervals, sometimes without but usually with a discoverable cause.

In the *rudimentary* or *larval cases,* termed by the French "les formes frustes," the four cardinal symptoms are absent but there is, notwithstanding, a long array of symptoms of hyperthyroidism. However, Barker's (*b*) word of warning is timely when he states that in our present knowledge of the autonomic nervous system "we must be more cautious than formerly in deciding that a given case with incomplete symptoms is really due to hyperthyroidism, for we now know that many of the symptoms met with in Graves' disease may be due to disturbances in other endocrin glands or to an irritation in local domains of the autonomic system." "Thus

tachycardia and epinephrin-glycosuria on the one hand, and sweating, diarrhea, pigmentation, lymphocytosis, eosinophilia on the other may occur in the entire absence of thyropathy." "Unless there is struma and increased vascularization of the thyroid gland (bruits) one should be cautious in assuming that the symptoms are due to hyperthyroidism." Maybaum objects, also, to the loose application of the term rudimentary or larval, since tachycardia alone may occur in hysteria, in disease of the medulla, in tabes dorsalis, etc., in conjunction with other suggestive symptoms; he, accordingly, would require that at least two of the cardinal symptoms be present in addition to suggestive minor phenomena before making a diagnosis of "forme fruste" of exophthalmic goiter. The French school also speaks of *"la forme maigre,"* or lean type, and *"la forme grasse,"* or fat type. The former are always more severe, while the latter usually do well. Some have suggested the term *"latent Graves' disease"* for cases without the exophthalmos or goiter. Thomson very properly objects to this nomenclature because such cases often present clinically just as severe a set of symptoms and often end fatally; they are much rather to be classed as "unrecognized" than "latent."

Finally, Plummer and Wilson, from their combined clinical and pathological studies of the rich material at the Mayo Clinic, have divided all goiters into (1) the non-hyperplastic atoxic, (2) the non-hyperplastic toxic, (3) the hyperplastic atoxic, and (4) the hyperplastic toxic varieties. Plummer (*a*) (*b*) admits that a considerable proportion of simple goiters, in fact 23 per cent, were grouped by him under the *non-hyperplastic toxic* because they had constitutional symptoms and that whether these were classed as simple or exophthalmic goiter depended upon how closely the clinical complex approached Graves' disease. He further states that he was the first to call attention to the fact "that an individual 22 years of age with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the 36th year so similar to the symptom-complex associated with hyperplastic thyroid that the best trained diagnosticians are constantly confusing the two conditions." Some clinicians are in the habit of speaking of this group as "Plummer's disease." However, we believe that while Plummer has certainly very emphatically called attention to this group, a careful perusal of Buschan's excellent monograph will reveal the fact that the latter also described a similar group in 1894.

Under the term *atoxic hyperplastic goiter* Plummer includes cases with a goiter that reveals on histological examination thyroid hyperplasia but no clinical evidence of Graves' disease, and under the *toxic hyperplastic goiter* he groups those cases with a definite clinical syndrome of Graves' disease and a histological thyroid hyperplasia. We believe that this classification of Plummer's is excellent and one that might be adopted by all clinicians and pathologists, at least for the present.

Diagnosis of Exophthalmic Goiter

The diagnosis of a typical case of exophthalmic goiter is one of the simplest in clinical medicine. The classical symptoms of tremor, tachycardia, vascular struma and exophthalmos can be recognized by even a junior medical student. On the other hand, the atypical cases with slight tachycardia and mild nervous disturbances are usually overlooked, because a careful examination is not made. It would perhaps not be out of place to discuss at this point what one would include under the term "exophthalmic goiter." Should all toxic hyperplastic goiters be included? Plummer (*a*) (*b*) answers this in the affirmative, though he admits the possible existence of a small group of cases which should not. It is quite possible that exophthalmos may occur with a non-hyperplastic toxic goiter, but if so, it is so rare that it may be considered accidental. We have accepted the position of Plummer, who believes exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid and sharply distinguished from the constitutional state that may develop with non-hyperplastic goiter. Both conditions are covered by the term *"thyrotoxicosis,"* but each is usually distinguishable from the other. However, as mentioned before, Plummer has also emphasized his belief that an individual of twenty-two years of age with an adenoma of the thyroid has a definite chance of developing during his thirty-sixth year a train of symptoms, so similar to the symptom-complex associated with the hyperplastic thyroid of exophthalmic goiter that the best trained diagnosticians are constantly confusing the two conditions. Apart from the chronicity of the course this group is further characterized by the relative absence of acute toxic symptoms as diarrhea, tachycardia, etc., the absence of exophthalmos and the slow development of symptoms of chronic cardiovascular disease.

Barker (*a*) recommends that the average practitioner consider the possibility of hyperthyroidism in every case in which he meets (1) tachycardia, (2) rapid emaciation, (3) excessive sweating, (4) persistent watery diarrhea without apparent cause, (5) the neurasthenic state, (6) outspoken lymphocytosis, (7) one or more of the ocular signs, and (8) fine tremor.

If the tachycardia does not subside with rest, if there is no ordinary heart lesion, and if there is a characteristic tremor with Stellwag's and Moebius' signs, emaciation, increased perspiration, insomnia and dyspnea on slight exertion, the diagnosis should be made without difficulty. That astute diagnostician, Pierre Marie (*b*), as long ago as 1883 wrote: "Each time one finds a permanent tachycardia and tremor without notable increase of temperature think of Basedow's disease: its existence will always be confirmed by the presence of one or several symptoms—diarrhea, generalized or localized sweating, bulimia, etc." The goiter, especially in goiter-districts, is not in itself a diagnostic sign except in the presence of

the vascular phenomena previously described in detail, namely the visible pulsation, the palpable systolic expansion, palpable thrill and audible bruits. Barker (*a*) points out that not every acutely developing goiter is an exophthalmic goiter: further, that the symptoms of Graves' disease may become superimposed on an ordinary colloid struma, termed by Marie "goître Basedowifié" and by Kocher "struma basedowificata."

The goiter heart of exophthalmic goiter is a thyreotoxic phenomenon and can usually be distinguished from the three types of heart which may arise from the mechanical effect of a simple goiter, viz.: (1) disturbances of the heart due to a struma extending through the superior aperture of the thorax (Kocher), (2) the goiter-heart due to a mechanical injury of the venous circulation (Rose's goiter heart), and (3) that due to interference with respiration (the dyspneic goiter heart of Kocher).

Exophthalmos of the characteristic kind with the protrusio bulbi and the various other ocular phenomena can be assigned only to the Graves' syndrome. It is unfortunately true, however, that cases of orbital tumor (especially chloromata), aneurism of the orbital artery and sinus thrombosis are too often mistaken for exophthalmic goiter because of the presence of a unilateral or even rarely of a bilateral protrusio bulbi. Increased intracranial pressure from hydrocephalus may also cause some exophthalmos. A careful examination of the eyes and of the pressure phenomena in these cases will lead to a correct diagnosis. Finally Barker and Hanes have reported exophthalmos with one or more of the allied ocular signs (anisocoria, von Graefe, Stellwag or Moebius) in sixteen out of thirty-three cases (48 per cent) of chronic nephritis without apparent involvement of the thyroid gland. It is true that twelve of these sixteen showed arterial hypertension (above 160 mm. Hg), but this was not, in Barker's opinion, the cause of the exophthalmos.

Differential Diagnosis.—There are two diseases that from their general symptomatology are sometimes mistaken for Graves' disease, namely neurasthenia and pulmonary tuberculosis.

Neurasthenia can usually be readily differentiated from mild Graves' disease by complete and repeated physical examinations. However, we must admit that the underlying factor in a considerable proportion of so-called neurasthenia can only be brought out by more or less elaborate laboratory tests. Harlow Brooks noted among the American troops at Camp Upton a high incidence of patients suffering from tachycardia with arhythmia increased by exercise and by the administration of epinephrin; next to the tachycardia emotional instability was the commonest symptom, while enlargement of the thyroid gland to some degree was present in 66 per cent of the cases. Further, there was frequently a family history of goiter, usually on the maternal side: lastly, he noted exophthalmos in some of the long standing cases. Brooks's observation could not be confirmed by Addis and Kerr, who divided the examined recruits into two groups—the first

with enlarged thyroids, of whom only 3.8 per cent had symptoms of neurocirculatory asthenia—the second those without enlarged thyroids, of whom 3.9 per cent had neurocirculatory signs. From this they concluded that the thyroid had no demonstrable etiological relationship with the neurocirculatory asthenia of soldiers. Further, Tompkins and his associates and Boas, by the determination of the basal metabolism and the response to ephinephrin, conclusively demonstrated that hyperthyroidism was not an underlying feature of the clinical syndrome known as neurocirculatory asthenia or the disturbed heart action of soldiers. Incidentally we might add the tremor is coarser and the heart has not such a tendency to enlargement in this group as in hyperthyroidism. In spite of this Harlow Brooks's contention was supported in 1919 by Pende (*b*), who wrote: "The war, in my opinion, showed clearly the importance of the constitutional hormonic anomalies." He speaks first of the emotive-commotive psychoneuroses of the soldier and next of the cardiovascular syndrome often referred to under the appropriate caption of the "irritable heart of the soldier." Pende noted two forms of dysharmonism in the war, one preeminently hyperthyroid and the other preëminently hypoadrenal. The contrast between the neurasthenia of civil life and exophthalmic goiter has been graphically drawn by Plummer (*d*).

In exophthalmic goiter there is usually an increased appetite; in neurasthenia, anorexia. The fluctuation of the symptoms in Graves' disease is marked by a periodicity of weeks or months and not by hours or days as in neurasthenia.

The short, quick, nervous step, the bright and prominent eyeballs, the mental alertness and physical restlessness of the sufferer from hyperthyroidism form a striking contrast to the ordinary picture of a pure neurasthenia. In both types of patients some sweating of the body surface and warm moist hands may occur, and indeed a subjective sensation of heat more often with (though at times without) a history of hyperhidrosis is the most characteristic symptom of the vasomotor group, but it should not be confused with the transitory hot flashes and cold sweats of neurasthenia.

Palpable thrills and audible bruits over the thyroid gland are present in eighty per cent of patients with Graves' disease, while they are practically never found in the uncomplicated neurasthenia.

Finally, hyperthyroidism results in an increased metabolism which nature attempts to compensate for by demanding more food, more water and more air.

Pulmonary Tuberculosis.—The differential diagnosis of mild thyroid toxemia and incipient *pulmonary tuberculosis* is by no means an easy task. Jennings points out that "certain cases of mild toxemia with cough and chronic pyrexia bear so close a resemblance to incipient pulmonary tuberculosis that a differential diagnosis may require a very close analysis

of all the clinical and laboratory findings." He considers that there are certain symptoms distinctive of each condition and again some symptoms common to both: the latter are fatiguability, tachycardia, pyrexia, cough and dyspnea, and derangement of digestion and metabolism. He, however, can offer no very great assistance in the differentiation of the two diseases. We may have to depend very largely upon the basal metabolism and Goetsch's epinephrin test for light in certain obscure cases.

Chlorosis.—Thyreotoxic Pseudochlorosis.—These conditions may present a problem in differential diagnosis. Wunderlich observed protrusion of the eyeballs in anemic-looking girls, which was often associated with pallor, fatiguability, emaciation and tachycardia. This clinical picture was supposed to be due to chlorosis; indeed, many of the earlier writers, notably James Begbie and J. W. Begbie, spoke of the "struma chloroticum." A blood examination reveals, however, a normal or even an excessive amount of hemoglobin and a normal number of red cells. Such patients in Mueller's opinion are no doubt the subjects of exophthalmic goiter.

Thompson calls attention to the possibility of mistaking the highly toxic clinical picture in which fever, acute dilatation of the heart, cardiac murmurs, dyspnea, precordial pain, delirium, sweating, edema, and an erythematous rash are present, for such acute conditions as *malignant endocarditis* or other forms of acute general septicemia. This is especially true when exophthalmos is absent or when the thyroid enlargement is not prominent. He quotes from his own experience two cases illustrating this point, and we must confess it would require a long continued critical observation of either case to make the differential diagnosis. However, the presence of embolic phenomena or the finding of one of the well known varieties of bacteria in the blood cultures should help to establish the presence of an ulcerative endocarditis.

Great assistance in the differential diagnosis of mild grades of hyperthyroidism from obscure cases of other nature can no doubt be obtained by certain *laboratory tests* as the determination of alimentary hyperglycemia and glycosuria, the basal metabolism, the epinephrin test of Goetsch, the acetonitril test of Hunt and the iodin test: these will be discussed at length in another chapter by an authority on this subject. Suffice it here to remind the reader that the white cell count invariably shows a relative and usually an actual increase in the mononuclear cells, especially of the so-called lymphocytes, but also at times of the large mononuclear cell of Ehrlich. We have learned to place a good deal of reliance on such a mononucleosis and regard it as at least suspicious evidence of hyperthyroidism and one calling for a careful revision of the clinical history and physical examination from a hyperthyroid angle.

Course and Duration

In some cases all the four cardinal symptoms appear more or less simultaneously, but more commonly one or two symptoms are first manifest; thus tachcardia, tremor, palpitation and some of the secondary symptoms may appear first to be followed later by exophthalmos and goiter. Sometimes exophthalmos is the first symptom to appear and sometimes the last. Most commonly the goiter is the first sign of the disease. Murray (*d*), in a series of eighty-seven cases in which the onset was recorded, found that the first symptom was goiter in forty-three, palpitation in nineteen, and exophthalmos in four. Plummer (*a*) found from an analysis of over one thousand cases of exophthalmic goiter occurring in the Mayo Clinic up to the year 1913 that the average order of onset of the most important symptoms was: (1) cerebral stimulation, (2) vasomotor disturbances of the skin, (3) tremor, (4) mental irritability, (5) tachycardia, (6) loss of strength, (7) cardiac insufficiency, (8) exophthalmos, (9) diarrhea, (10) vomiting, (11) mental depression, (12) jaundice, (13) death. The course of the disease is essentially a chronic one and varies from ten to twenty or more years. Very rarely the duration may be measured by weeks or even days. Exacerbations may come on suddenly, due to various causes as infection, mental shock or physical exertion.

In a large number of cases, as W. G. Thompson has so graphically described, sooner or later an acute febrile toxemia develops, in which, in addition to the cardinal symptoms of goiter, fever of 103° to 104° F., acute dilatation of the heart with murmurs, rapid pulse, dyspnea, precordial or abdominal pain, gastro-intestinal crises, edema of the legs, sweating and sometimes erythema make their appearance. Such attacks of acute hyperthyroidism usually follow some mild intercurrent infection as tonsillitis, quinzy, influenza or bronchitis. It may subside in the course of several weeks or it may result in death from the resulting cardiac insufficiency.

Relapses are not uncommon in both the medically and surgically treated.

C. H. Mayo admits that they occur in ten per cent of those cases which have undergone some form of surgical treatment.

Trousseau speaks of six relapses and Graves of three as having occurred in patients before the days of surgical treatment of the disease. A relapse may occur years after an apparent recovery from the disease; of course in such a case the question can be raised:

Are these true relapses or merely recrudescences of the disease which has never really subsided?

Prognosis

The prognosis is more favorable in children than in adults; some recover completely whilst in others slight struma and exophthalmos remain. It is better in the female than the male, because the physical exertion of the former is never as great and more readily controlled. The social position is of considerable importance, by which we mean a patient with private means is not compelled to return to his work too soon, and there is usually, in consequence, less mental anxiety. Apart from the above considerations the prognosis depends upon (1) the mode of onset, (2) the severity of the symptoms, (3) the duration of the disease, and (4) the amount of damage already suffered by the circulatory system. Symptoms of grave omen are progressive emaciation, much prostration, great tachycardia, anorexia, continued vomiting, severe diarrhea, dyspnea and severe muscular tremor.

In any case, however, a guarded prognosis must necessarily be given. While there is a general belief among physicians that patients with exophthalmic goiter never recover and yet never die, except following surgical operations, it would be much nearer the mark to say that few recover and some die. A relatively complete return to health is not rare, so that the patient may be able to resume his work or domestic duties: but such a patient is not perfectly well and, in my experience, always reveals some evidence of the disease, as nervousness, a slight increase of the pulse rate and exophthalmos. Indeed, some degree of exophthalmos is the most constant residual sign even in those cases treated surgically. Further, modern laboratory methods have shown that the metabolic rate will also show a persistent level above the normal even in cases which otherwise show marked subjective improvement.

There can be no doubt that cases which *early* submit to operative treatment show a more marked and more complete recovery than is evidenced in those who postpone surgery indefinitely and try one after the other of the various medical procedures.

C. H. Mayo (*h*) believes that surgery, aided by medical treatment, cures exophthalmic goiter in seventy per cent of cases; or, in other words, seventy per cent feel well enough to attend to the ordinary business affairs of life and even forget that they have been sick.

Twenty per cent of these so-called "cured" cases still show slight widening of the palpebral fissure, which, while not realized by the patient, is noticeable to the trained physician. Further, in Mayo's experience sixteen per cent are noticeably improved but are not quite well in that they have some symptoms that remind them of the necessity of being careful. Another four or five per cent have the progress of the disease checked but too late to overcome the permanent degeneration of the essential

organs. The immediate operative mortality at the Mayo Clinic is about three per cent, while another two per cent die of degeneration incidental to the disease or from some intercurrent disease made possible by the lowered vitality resulting from the thyrotoxicosis.

The actual mortality is variously given by different authorities: Thus Buschan gives 11.6 per cent, Sattler 12.5 per cent, Mackenzie 24.5 per cent, and Hale White 39 per cent. Osler points out that statistics are misleading as only the severe cases come under hospital treatment. Further, as Dock adds, the actual death rate is nearly impossible to determine because first there is great variation in the severity of the symptoms, second a relatively large number of the severe cases is reported, and lastly death is often due only indirectly to the disease itself and more often to complications or accidentally associated diseases. However, we believe that Mackenzie (*c*) is not far from the mark when he writes: "In about 25 per cent of the cases death results from the disease; in about 50 per cent, more or less complete recovery will eventually take place. In the remainder the disease continues in a chronic form during life." That exophthalmic goiter plays a considerable economic rôle is shown by the fact that during the four years 1911-1914 in England and Wales 1558 women and 155 men died of exophthalmic goiter; the maximum age period at the time of death was between the thirty-fifth and fortieth year.

Among the *causes of death* cardiac insufficiency is the most frequent; then comes exhaustion from vomiting, diarrhea, fever and other toxic phenomena. About half the fatal cases succumb to some intercurrent disease; pneumonia, bronchitis and pulmonary tuberculosis are frequent terminal infections. The end may be sudden and due to syncope even when the patient is getting on well.

Treatment of Exophthalmic Goiter

The number of modes of treatment of exophthalmic goiter is legion. This, of course, is a certain indication that no one form of treatment as yet devised is causal or specific. Even the various surgical procedures must be regarded as symptomatic though we are not yet prepared to accept the ultra-conservative view of Bram (*a*) (*b*), who states that "the large majority of cases are curable by non-surgical procedures," and again that "the disease is one strictly outside the domain of surgery unless dangerous pressure symptoms or malignant changes set in."

We will, for purposes of convenience, consider treatment under I *General measures,* including (1) rest, (2) fresh air, (3) hydrotherapy and electricity, (4) dietetic, (5) medicinal, (6) organotherapy, (7) serum therapy, and II *Local measures,* including (1) cold applications, (2) X-ray and radium, (3) injections in the gland, (4) the surgical procedures

of ligation of one or more vessels, lobectomy or thyroidectomy and sympatheticotomy.

General Measures.—*Rest.*—Both physical and mental rest is clearly indicated for the important symptoms of muscular weakness, the disordered heart action, the nervous irritability and the increased metabolism. Of course the degree of rest must be determined for each type of case. In the severe intoxication a rigid Weir Mitchell rest-cure is indicated; this implies isolation in a hospital, preferably in a separate room, with a tactful, patient and well-trained nurse in charge; complete bed rest must be insisted upon with only the mildest of relaxation as reading, knitting or basket-work. All visitors, letters, business worries and household cares must be excluded. In the milder cases bed rest should be required at fixed hours when possible, and when not possible the patient should be ordered to go to bed as soon as the day's work is over. Late hours must be prohibited, and if on occasion they are necessary, they should be preceded and followed by a rest of sufficient length to compensate for the loss sustained. The patient should be instructed to lie down rather than to sit, to sit rather than to stand, and, above all, to avoid stair-climbing as far as possible.

Exercise should not be permitted at first; massage and passive movements may be substituted for a time. Moderate massage is useful in cases in which absolute rest in bed is necessary. After distinct improvement has been noted, gradually increased exercise should be encouraged. Detailed instructions as to the kind and amount of exercise must be given to the patient, based upon the amount of work necessarily called for by his mode of life. Both work and exercise should stop short of fatigue. It is well to advise against coitus.

Mental rest is just as necessary as physical. In the severe cases rigid seclusion is advisable; in the less severe an avoidance of all unnecessary activity must be enacted; necessary occupations can be followed and cheerful companionship should not be shunned; however, exciting and depressing occupations should be given up, temporarily at least. A change of scene, as a visit to Europe, to the Bermudas, Southern California or Florida, is often helpful, provided the patient travels by easy stages and in a leisurely manner.

Fresh Air.—Fresh air is an essential of the rest treatment. The bed room should be well aired or, better still, the patient should sleep out of doors on a sleeping porch. During the day the milder case should be encouraged to walk or drive or, in the event of these being too tiring, he should be encouraged to sit out of doors well protected from cold and wind. As far as climate is concerned, the ideal one includes moderate elevation (1,500-2,000 feet), pure cool air, and a freedom from much wind. The seashore and high altitudes are not well borne because of the cardiac and nervous symptoms. However, no rule can be laid down where a

patient with exophthalmic goiter will be most comfortable; the patient's own experience is of greater importance. Tight lacing and tight collars should be taboo.

Hydrotherapy and Electricity.—Both these physical therapeutic measures have been used, but with varying results. However, exhausting and depressing baths should be avoided. A daily warm bath at 98° to 100° F. should be insisted upon. Warm sea water or salt baths are sometimes useful but bathing in the open sea is generally to be forbidden.

Electricity has been much used in the past with excellent results if the reports can be believed. Some, as Benedict, von Dusch and Chvostek, prefer galvanism; others, as Vigouroux and Murray, faradism; still others recommend static electricity, while a few recommend the high frequency current. It would seem to us that the chief benefit in these procedures is through mental suggestion. Nevertheless such a well known clinician as Murray (*b*) believes that he has "observed steady improvement and practical recovery take place in several cases in which this treatment has been systematically carried out."

Diet.—The diet should be as varied and as palatable as possible to encourage the patient to increase the body weight or at least to regain weight lost through the increase of the metabolic processes inherent in the disease. As overfeeding is to be carefully avoided frequent small meals are to be preferred to three large ones. All indigestible food and condiments must be prohibited, and tea and coffee allowed only in very small quantities. Alcohol and tobacco had best be excluded.

The majority of the older writers and more recently Ochsner favor the use of a low protein diet—namely milk, cream, buttermilk, cooked vegetables, stewed fruits and eggs. Janney's (*b*) few metabolic experiments made on patients with exophthalmic goiter do not substantiate this view. He believes that this point is clearly brought out by the experiments of Pribram and Porges, who found the respiratory quotient of the disease unchanged by a low protein diet; on the other hand, a high protein diet with restriction of the carbohydrates but of the same caloric value, produced an increase in the basal metabolism and a loss of weight. The best results were obtained with a *mixed diet.* Janney believes that a certain but not necessarily a predominant amount of carbohydrate in the diet is useful in combating the nitrogen loss; he found that the most favorable diet was one in which the protein, fat and carbohydrate are present in the usual proportions but in increased amounts.

Medication, Galenical.—Various preparations of iodin as the syrup of hydriodic acid, iodipin and the iodids were formerly much in use and were believed to reduce the size of the thyroid gland. However, a diminution in the size of the gland, even if it did occur, did not mean a reduction of the hyperthyroidism; therefore while a small minority of the patients were improved, the great majority were made worse as shown

by an increase in the nervousness, headache, palpitation, etc. The red iodid of mercury which was once so popular as a local application is now discarded. Injections of iodin and iodoform into the gland substance are very dangerous and have been practically abandoned. Breuer of Vienna and Gautier of Geneva (quoted by Moffitt) have reported the development of exophthalmic goiter after the treatment of simple goiter with iodin preparations. Theodore Kocher (*h*) has reported a similar case under the title "Iod-Basedow," and speaks of its great frequency; he advises against the use of iodin internally or externally even in simple goiter, or, if it be used at all, that it be administered only in small doses for a short period.

G. R. Murray frankly admits that "the number of drugs that have been recommended in the treatment of this malady is large but as far as my experience goes I have found only a few to be of special service." For many years belladonna, either as the tincture or its alkaloid atropin, had a great vogue because of its well known antagonism to such external secretions as the saliva and sweat; ten to fifteen drops of the tincture or one one-hundred-and-fiftieth of a grain of atropin were given three times a day until symptoms of atropin poisoning supervened. It certainly lessens the sweating and appears to soothe the nervous system and to diminish the excitability and restlessness as well as to quiet the heart. In our own experience it has proved of some comfort to the patient, though we are quite skeptical as to its lessening the thyroid secretion in man and know of no animal pharmacological experiments in support of a supposed restraining effect on the thyroid internal secretion.

Quinin was formerly used by Friedreich. More recently Forchheimer has recommended the exhibition of quinin hydrobromate in doses of two to five grains in combination with one grain of ergotin three times a day. The former should stop when cinchonism appears. It would seem that some benefit is experienced by the patient with mild symptoms of hyperthyroidism from this combination of drugs. We use it almost as a routine while the patient is undergoing the rest treatment prior to surgery.

Various preparations of the bromides including the strontium and calcium salts in daily doses of thirty to forty-five grains have been used with some benefit. Some clinicians, following the work of McCarrison (*e*) on the etiology and treatment of endemic goiter, have given intestinal antiseptics as salol and thymol, in the hope that Graves' disease is the result of a general infection, the portal of entry of which lies in the intestinal tract. However we know of no successful results.

Before leaving this section we must consider the various measures to combat particularly *troublesome symptoms.* For the tachycardia and palpitation bed rest is the first essential; of great assistance is a light ice bag placed over the precordia and kept constantly or intermittently applied, according to the desire of the patient. Rarely are cardiac stim-

ulants necessary except when there is evidence of cardiac decompensation, which occurs only late in the disease or in very acute cases. Digitalis in Graves' disease is very apt to produce cardiac arhythmia and troublesome gastric irritation, and on this account even when indicated because of a dilated heart should be given in small doses every other day, and preferably in the form of the powdered leaves, digitalin or digipuratum. In mild cases of cardiac weakness five to ten drops of the tincture of strophanthus are well borne and fairly efficacious. Strychnia may also be tried. For the nervous phenomena rest, fresh air and a comfortable bed do more for the patient than drugs. A warm bath at 95° F. given just before retiring for the night is very quieting, particularly when followed by a hot drink or a hot water bottle to the feet. If in spite of these measures insomnia persists a full dose of bromid or better still of veronal may be given at bedtime. Pure hypnotics as chloral and opiates should be avoided.

For the gastro-intestinal irritation regulation of the diet usually suffices. Nux vomica or strychnia are useful for improving the appetite and stimulating the gastric juice. Constipation should be met by diet, water-drinking and regular habits, and when these do not suffice a mild laxative as cascara sagrada or sodium phosphate. Traczewski and Kocher formerly thought that sodium phosphate was almost a specific in the treatment of exophthalmic goiter. This view is no longer tenable.

For the gastro-intestinal crises lavage, catharsis and enemata are indicated. A simple diet of albumin water and peptonized or boiled milk should be used for a few days. Bismuth and salol may be tried in appropriate doses, but opiates and astringents should be avoided.

The anemia is rarely severe enough to require iron and arsenic. Fever, when marked, can be treated by sponging with tepid water or in selected cases by tepid full baths or even cold full baths.

For the conjunctival and corneal irritation a boracic acid solution usually suffices except in very severe cases when special treatment with other drugs may be necessary.

Organotherapy.—Some of those who believe in the theory of an altered secretion (dysthyroidism) rather than an increase of the normal secretion (hyperthyroidism) as playing the dominant etiologic rôle highly recommend the administration of the fresh or desiccated thyroid gland. Dock (*a*) tried it in nine cases with a certain amount of success in some. Mackenzie suggests that thyroid extract may be useful in old cases with signs of hypothyroidism. It is nevertheless true that freshly made and active preparations of thyroid gland will produce in the great majority of exophthalmic goiter patients an increase in their symptoms and sometimes to an alarming degree. Accordingly, in light of our present knowledge and experience, the use of thyroid preparations in uncomplicated Graves' disease should be discouraged.

Upon the supposition that the enlargement of the thymus so frequently found in Graves' disease is a compensatory phenomenon, thymus extract was tried by Mikulicz, Solis-Cohen, Mackenzie and others. Mackenzie (*b*), who gave it an extensive trial in twenty cases, noted no appreciable effect, and goes still further when he states that he has not found any special virtue in any of the gland preparations, separately or combined, in the treatment of exophthalmic goiter.

Gibson believes that the suprarenal extract has "no rival in the management of the affection," and states that the rate of the pulse is reduced, the protrusion of the eyeballs disappears, the thyroid gland diminishes, the tremor along with every other nervous symptom vanishes and the patient is restored to health in a way that we never see from any other method of treatment. While it is true that other clinicians have not proved so enthusiastic about the gland extract, a short trial at least is in our opinion worthy of consideration.

Extracts of the pituitary gland have also been tried and may benefit some of the minor phenomena as the fever, polyuria, polydipsia, the fat deposition, etc., but, in the opinion of Hofstaetter and others, have no effect upon the cardinal symptoms of the exophthalmic goiter.

The spleen, ovarian and testicular extracts have also been tried from time to time but without the slightest success.

Serum Therapy.—In 1895 Ballet and Enriquez endeavored to neutralize the poison of the thyroid in nine cases of exophthalmic goiter by administering the serum of thyroidectomized dogs and reported an improvement in the tremor, exophthalmos and struma. Lanz made similar attempts with the milk of thyroidectomized goats and sheep. Burghart used the blood of a myxedema patient, Moebius (*c*) the thyroid of a cretin. Soon the manufacturing chemist prepared for clinical use several remedies of this class, for example the "antithyroidin" of Moebius (dose 0.5 to 4 c.c. three times a day), which was made from the serum of thyroidectomized sheep: also "rodagen" (dose 5 to 10 grams daily), which was prepared from the milk of thyroidectomized goats, and lastly "thyroidectin" (dose 5 to 50 grains three times a day) made from the blood of thyroidectomized sheep. The supposed effects of these various preparations are about the same; the struma becomes smaller and softer, the tachycardia is lessened and the mental irritability and the muscular weakness are sometimes improved, though more often not. In a few patients the improvement is prompt, but in the majority the progress is slow. Further, the dosage is a matter of guesswork since we do not know how much toxin has to be neutralized nor how much antitoxin there is in a given amount of the preparation. It is possible that the isolation of the active principle of the thyroid gland in a pure chemical form as has been done by Kendall will be the first step in overcoming such difficulties. For the present if one wishes to try these remedies one must

increase the dosage as rapidly as possible to a point where there is either a marked improvement in the symptoms or signs of intolerance on the part of the patient when one should stop altogether, continue or decrease the dose according to the result. Rodagen and antithyroidin are not well borne, the former on account of the odor, the latter on account of the phenol used as a preservative. Thyroidectin is less disagreeable to the patient. Further, all these preparations are expensive and the results as yet are not very encouraging.

Mackenzie states that Merck's serum and thyroidectin are inert and expresses the belief that casein would have the same effect as rodagen. However, after an extensive trial of rodagen, Mackenzie admits that it was of distinct benefit in some cases of exophthalmic goiter.

Various attempts to produce thyrotoxic sera have been made by Portis, MacCallum (*a*) and Yates but without success. A different method from any of the above was used by Murray (*e*) and subsequently by Beebe (*a*). The latter obtained a cytotoxic serum by injecting into rabbits the nucleoprotein and the thyreoglobulin precipitated from the thyroid gland of exophthalmic goiter patients obtained at first from the autopsy room, but later from the operating room. Beside this "pathological serum," a "normal" cytotoxic serum was prepared in the same way from the normal human thyroid. Rogers believes that Beebe's serum has a twofold function: (1) a late and cumulative effect in suppressing the action of the thyroid secreting cells and (2) an antitoxic or nullifying action against the excessive thyreoglobulin. They do not believe that this serum will cure all cases and were very cautious at first in promising results. "Technical difficulties make the preparation of the serum on a commercial scale improbable. A very skillful chemist experienced in biologic work is a necessity." This form of serum therapy is of course based on the theory that exophthalmic goiter is a toxemia and that the toxin in question is the thyroglobulin. Rogers and Beebe state that there are two types favorable for treatment: (1) cases in the early stage of the disease, whether of the mild, severe or the acute toxemic type; (2) long standing cases of the subacute variety with occasional exacerbations but without marked secondary changes. After the injection of the serum in the usual dose there may be a local as well as a general reaction with increase in the temperature and pulse rate, restlessness, nausea and vomiting. Though in several cases there were severe and even alarming reactions, the authors have never known of a fatality from the use of the serum. Beebe (*a*) and Rogers in 1909 had treated more than five hundred cases of exophthalmic goiter, of which 20 to 25 per cent of the patients were cured, 30 to 40 per cent were distinctly improved, 30 per cent somewhat improved and 10 per cent quite unaffected.

Local Measures.—*Cold.*—*Application of cold* either in the form of cold compresses wrung out in ice-water, a Leiter coil or an ice-bag to

the thyroid gland has long been employed, with the hope thereby to reduce the vascularity of the gland and so diminish the excretion of the normal or perverted gland substance. It is still to be recommended in the general medical management of a case of exophthalmic goiter.

X-rays and Radium.—With the same end in view the röntgen rays have been recommended. C. H. Mayo (*c*) believes that they lessen vascularity and induce sclerosis around the gland and so diminish the risk of hemorrhage at operation. Freund, Cook, Seymour, Pfahler, and Grier are among the many who have published their results from this form of treatment. Some are very conservative, others extremely radical in their claims. Seymour reports an improvement in seventy-three of eighty cases treated with the target ten inches from the skin and one thickness of sole leather interposed; he recommends the production of only a slight erythema but without skin irritation; the dose is repeated in three to four weeks.

Pfahler and Zulick believe that the röntgen rays should be given a trial in all cases of Graves' disease, because no harm is done and an operation may thus be avoided. They insist that both the thyroid and thymus glands should be rayed. An increase in body weight and a decrease in pulse rate are the first signs of improvement. The struma and exophthalmos are the last to manifest retrogression and in some cases show no appreciable change. They warn against too prolonged treatment because of the possible danger of hypothyroidism resulting.

Grier claims to have cured 87.5 per cent of sixty-three cases of hyperthyroidism treated by him. The most favorable results were noted in simple hyperthyroidism, acute and chronic exophthalmic goiter; the Basedowized goiter yields much less readily to this form of treatment. Waters (*b*) reported his results in sixty cases and believes a more liberal use of this form of therapy worthy of trial. Even such a conservative surgeon as Halsted (*e*) has tried X-ray treatment of the thymus gland in six cases of exophthalmic goiter refractory to double lobectomy with astonishingly good results. In contrast to the above enthusiasm Mackenzie (*c*) expresses frank disappointment with the results in Graves' disease but admits that the trend of present experience is decidedly in favor of its further trial. Murray (*g*) writes that "the application of suitable doses of X-rays to the enlarged thyroid gland has in some of my cases proved to be of great value. The gland gradually diminishes in size and the other symptoms subside. Atrophic changes in the secretory epithelium and both interstitial and intracapsular fibrosis appear to be induced by the action of the rays." While fifteen to twenty weekly doses usually suffice, Murray advises in the obstinate cases a persistence with the treatment for a year at least.

In conclusion we believe that any one who reads Ludin's analysis of

two hundred and eight papers on this subject will agree that the treatment in selected cases is worthy of further trial. We believe that it is a procedure to be recommended in the simple cases of hyperthyroidism and possibly as a preliminary and preoperative measure in the very vascular struma of certain cases of exophthalmic goiter and lastly as a postoperative measure in cases refractory to lobectomy.

The use of radium was first recommended by Abbé, who introduced it directly into the gland substance but without distinctly beneficial results. However, Turner has applied it externally in fifty cases of Graves' disease with distinct success in all but one case. The patients gained in weight and strength, while the tachycardia, tremor and dyspnea diminished or disappeared. The thyroid gland, Turner states, becomes harder but usually not much smaller, while the exophthalmos is but little affected. Each lobe as well as the isthmus of the thyroid should be treated with a dose for each of 200 to 400 milligram hours, with of course proper screening: this dosage can be repeated in three months. The advantages of radium are, first, a more exact dosage can be given than with the X-rays, secondly, radium penetrates better and thirdly is not so disturbing to the nervous patient.

Injections Into the Gland.—The injection of boiling water into the thyroid gland has been practiced by Porter and O'Day and C. H. Mayo (*g*). Porter (*a*) (*b*) has been using the method since 1911 and has treated more than one hundred cases; he considers it indicated in patients with small thyroid glands and mild hyperthyroidism, or after a lobectomy for recurrence of hyperthyroidism in the other lobe and in patients with large goiters and extreme symptoms of hyperthyroidism until they become safe surgical risks. O'Day (*b*) has used this method in seventeen cases of hyperthyroidism, though he admits that partial thyroidectomy is the procedure of choice. For the exact technic we refer the reader to the original articles and to the textbooks of surgery.

Watson recommends the intrathyroid injection of quinin and urea hydrochlorid, which he has performed in over one hundred cases of goiter without untoward effects. He recommends a preliminary injection of the goiter with sterile saline solution after carefully using novocain as a local anesthetic to overcome the tendency to hyperthyroidism from the pain of the injection. He then injects one to four mills of the 30 to 50 per cent quinin and urea solution every third day: he has found eight to fifteen infiltrations are necessary. He recommends it only for the relief of the hyperthyroidism and not as a cure of the goiter itself.

Surgical Procedures.—After carefully reading Halsted's (*f*) "Operative History of Goiter," it would seem that the first authentic excision of the thyroid gland for exophthalmic goiter was by P. H. Watson, who in 1874 reported five thyroidectomies, three of which were for definite cases of Graves' disease. In 1877 Lister, according to Mackenzie (*c*), did a par-

tial thyroidectomy to relieve dyspnea in a case of exophthalmic goiter. In 1880 Tillaux, according to Benard, performed a successful thyroidectomy for Graves' disease. Rehn (*a*) in 1884 contributed a paper which is usually considered the earliest one in this special field. The pioneers in this field of surgery, Theodore Kocher, J. L. Reverdin, Halsted, C. H. Mayo and Crile, have published such statistics that we are forced to admit that surgery is at least of symptomatic benefit. The physician has for years been rather skeptical about the value of surgery in Graves' disease, while ready to admit that if there be hyperfunction of the thyroid, a removal of the hyperplastic tissue or at least reducing it in amount would cure the disease; however, internists have pointed out that one cannot remove the entire thyroid gland, and that one cannot know when a part is removed whether the remaining portion is not relatively more dangerous; lastly they recall how hypertrophied tissue may keep on growing or even grow more rapidly if partially removed. Bram (*a*) in a recent paper gives the various objections of the extreme conservative against thyroidectomy and any of the later modifications of the surgical treatment of Graves' disease. While not prepared to accept this ultra-medical point of view, we believe it is a paper that should be read by internist and surgeon alike. The immediate effect of the operation is invariably an exacerbation in the symptoms of hyperthyroidism, which sometimes proves so severe as to result in death in a few hours after operation. However, after the first few days, there is commonly marked improvement in the entire syndrome, usually first seen in the tachycardia and other cardiac symptoms and shortly in the tremor and other nervous symptoms. Even the exophthalmos is said sometimes to disappear, though we personally have never seen this event.

The part of the gland that has been left behind does not always hypertrophy; indeed, Kocher, Reverdin and Mayo state that it more often contracts. Nevertheless, in a considerable proportion of cases hypertrophy does occur with a return of the symptoms, necessitating a second or even a third operation. Postoperative recovery does not always occur; the earlier statistics showed a death rate of over 12 per cent in all types of cases and as high as 22 per cent in the more severe cases. Death due to operative procedure depends upon the condition of the patient, but still more upon the skill and experience of the surgeon. In Rehn's (*b*) series of 177 cases collected from the literature in 1901 the operative mortality was 13.6 per cent. In marked contrast are the statistics of Kocher (*d*), who in his first 176 cases had a mortality of only 4.5 per cent; Crile reports a series of 206 consecutive thyroidectomies and 87 ligations without a goiter death, the one death in his series being due to a double pneumonia. C. H. Mayo (*h*) has performed 278 consecutive operations in exophthalmic goiter without a death. These figures are due in part to the remarkable progressive improvement in the technic of the surgical art, and

in part to the practice of the two or three stage operation in the more severe cases.

The indications for operation in exophthalmic goiter should be clearly understood by the internist and surgeon alike. Cases of so-called Basedowized goiter, in which there is a mechanical compression of the struma, are clearly in need of surgery. Further, in the absence of any contra-indication, a patient with the typical syndrome which has not yielded to a few weeks of good medical treatment should be advised to submit to an operation. It is much harder to decide as to whether or not surgery is indicated in the so-called atypical cases and in those which have improved under medical treatment without getting well. Surgery is, at least for a time, contra-indicated in emaciated patients with extreme exophthalmos or advanced myocardial degeneration and also when there is reason to suppose there is developing an acute exacerbation of the symptoms. Mayo (*a*) does not operate if the pulse be above 130 per minute, or irregular in force or rhythm or if there be anemia or edema present; for such cases he recommends the use of belladonna internally and the röntgen ray locally. Kocher (*a*) warns against surgery in patients with low blood pressure or periodic attacks of delirium cordis.

The operations most in use at the present day are partial resection of the thyroid gland or ligation of one or more of the thyroid arteries. In early or mild hyperthyroidism or very severe cases of exophthalmic goiter with secondary symptoms, ligation is often a preliminary measure and indeed may suffice. In a later paper Mayo (*c*) recommends a preliminary ligation with thyroidectomy four months later when the heart is dilated more than one inch in its percussion outline. In 225 cases so treated by Mayo the mortality was only 2 per cent, while fifty-nine per cent were reported very much improved several years later. Balfour, of the Mayo Clinic, advises the removal of the entire right lobe, the isthmus and part of the left lobe of the thyroid as the usual procedure: in other words, four-fifths of the gland should be removed to give the best results. This is not the place to give surgical technical details, which will be found in all special treatises of regional surgery.

There is some difference of opinion as to the choice of anesthesia. Kocher and for a time Halsted preferred local anesthesia. Mayo recommends general anesthesia with ether on the open mask and so avoids surgical shock: in his opinion the struma in Graves' disease is rarely large enough to make general anesthesia a dangerous procedure. Crile prefers nitrous oxid general anesthesia combined with novocain local anesthesia: he believes that nitrous oxid as compared with ether anesthesia protects more against shock because of its interference with the use of oxygen by the brain cells. Crile's "anoci-association method" is possibly unnecessarily elaborate but has for its object the lessening of the elements of fear and shock in the production of hyperthyroidism. In

his article in 1913, he writes: "The ideal plan of approach, at least in my experience, is to assure the patient that hers is a curable malady, that it can be treated in a hospital, and that non-operative measures will first be tried; then if they prove inadequate a simple operation will be done, that it will be best to leave the decision to the judgment of her medical adviser, and that since even the discussion is both unpleasant and injurious it would be best not to open this subject again. The patient usually gladly consents to leaving the whole matter to the judgment of the physician and the way is then opened for the most effective treatment which in my judgment has ever been proposed—namely, ligation or excision on the new principle of anoci-association. The patient has received no psychic stimulation arising from the knowledge of the imminence of the operation and none on being anesthetized and finally no afferent impulse reaches the brain from the field of operation."

In the postoperative period vomiting and secondary hemorrhage are particularly to be feared. The latter is to be avoided by the most careful ligation of all vessels and subsequent observation of the wound. The postoperative hyperthyroidism, manifested by tachycardia, bounding pulse, insomnia, vomiting and diarrhea, must be promptly met by the hypodermic administration of epinephrin, atropin and morphin and by absolute quiet and avoidance of visits from importuning friends. Postoperative tetany was formerly not infrequent, owing to injury to the parathyroid glands; the risk has been largely removed by the so-called "intracapsular operation," which also lessens the likelihood of injury to the recurrent laryngeal nerve. C. H. Mayo has noted only one case of postoperative tetany in 3203 goiter operations, and in this patient some of the diagnostic points of tetany were wanting.

Postoperative treatment along general and hygienic lines should be continued until the patient is restored to comparative health. Ochsner gives his patients very specific directions, a practice which might be followed by all surgeons to great advantage. As Crotti states, "When once a patient has been operated on he becomes again a medical patient." He should be asked to report for further examination upon the return of any of the serious symptoms of the disease.

Just a word about the other surgical procedures that have been advised from time to time in the treatment of exophthalmic goiter.

The "exothyreopexy" of Poncet, as described by Jaboulay, consists of the exposure and fixation of the enlarged thyroid gland in the wound where it is left to shrink under an aseptic dressing. In the opinion of the majority of surgeons it is as dangerous and less efficient than the other surgical procedures.

Sympathectomy or resection of the sympathetic ganglion has sometimes given good results, but also many failures. Jaboulay in 1896, following the suggestion of Trousseau, was the first to introduce an operation on

the sympathetic ganglion for the relief of exophthalmic goiter: this method was also practised by his pupils Abadie and Jonesco. Later Jaboulay modified this procedure for the relief of the exophthalmos and by removing the superior or sometimes the middle ganglion procured slight ptosis of the upper eyelids with a slight improvement in the unsightly exophthalmos. However, the procedure has been largely abandoned both as a measure to treat the disease and to lessen the exophthalmos.

Thymectomy with or without thyroidectomy was for a time resorted to, but with such a high mortality that it was discarded. More recently it has been quite enthusiastically recommended by Capelle and Bayer from Garré's clinic in Bonn and with more caution by Halsted (*c*) of Baltimore. The rationale of the procedure has been discussed on page 351 et seq. Suffice it to say that the number of cases in which thymectomy has benefited either with or without a coincident strumectomy, is as yet too few to warrant any definite conclusions.

One must also mention the local treatment of the tonsils, nose and throat upon the assumption that in them may be lodged the primary focus of infection. Thus Bergh believes that the infection spreads from the nasopharynx along the lymphatics to the thyroid gland; he believes that he has seen at least eleven cases of his own and refers to Salling, who found a similar focus of infection in thirteen patients in a series of ninety-seven cases of exophthalmic goiter. Bergh collected forty-two additional cases from the literature. He recommends massage of the nasal mucosa, as well as the other necessary operative procedures.

Resection of the colon was recommended by Arbuthnot Lane in both exophthalmic and simple goiter on the grounds that there is an infection of this organ which is the primary cause of the goiter. This theory of the origin of goiter has been adopted by McCarrison (*d*) but has not been generally accepted. McCarrison, however, recommends the administration of laxatives and the intestinal antiseptics and not surgery.

Finally a word as to the end results of the surgical treatment of Graves' disease. Mackenzie (*e*) writes that "my own experience of operation in exophthalmic goiter has on the whole been very unfavorable: in St. Thomas Hospital of London there were three deaths in fifteen cases of ligation of the poles and eight deaths in nineteen cases of thyroidectomy: further, of the twenty-three patients who survived the operation there was no change for better or worse in twelve cases." If such discouraging results were universal surgery would rapidly fall into disfavor. However, Klose has collected the statistics of the surgical treatment of exophthalmic goiter by various surgeons published between the years 1896 and 1912: the percentage of cases of cure or at least marked improvement ranged from fifty to ninety-eight. Mackenzie is more convinced of the accuracy of Halsted's figures, which admit of an approximate cure in sixty per cent of cases, in sixty to eighty per cent of which

there remain symptoms of overactivity of the thyroid gland sufficiently pronounced to be detected by the expert clinician. Judd and Pemberton, from an analysis of the results in one hundred and twenty-one cases six years after operation at the Mayo Clinic, report a cure in about forty-five per cent, a practical cure in twenty-three per cent, although a slight trace of the old trouble may persist: four per cent obtained some benefit, while five per cent reported that they had received no benefit. Finally, such a well known medical authority on exophthalmic goiter as G. R. Murray (*b*) concludes that "the results are most encouraging and indicate that an operation offers a good prospect of affording relief."

Hypothyroidism and Cretinic Degeneration . . . . . .

. . . . . *Nelson W. Janney*

Sporadic Hypothyroidism—Historical—Definition and Nomenclature—Geographical Distribution—Etiology—Pathology—Metabolism—Symptomatology—Diagnosis—Differential Diagnosis—Prognosis—Treatment—Illustrative Cases—The Cretinic Degeneration—Definition—Historical—Geographical and Orographical Distribution—Prevalence—Economic and Military Importance — Endemiological — Epidemiological — Etiology — Theories as to Etiology—Pathology—Symptomatology—Diagnosis—Treatment.

Hypothyroidism

NELSON W. JANNEY

LOS ANGELES

HISTORICAL
DEFINITION AND NOMENCLATURE
GEOGRAPHICAL DISTRIBUTION
ETIOLOGY
PATHOLOGY
METABOLISM
SYMPTOMATOLOGY
DIAGNOSIS
PROGNOSIS
TREATMENT

Sporadic Hypothyroidism

Historical

Although endemic goiter and cretinism have been known certainly since the times of the Romans, the recognition of sporadically occurring hypothyroidism is comparatively recent. No distinction in early accounts can be drawn between endemic and sporadically occurring cretins which were confused with various diseases exhibiting nanism and imbecility. Curling in 1850 described cases of sporadic cretinism. Myxedema was first described as a clinical entity without recognition of its true etiology in the decennium 1870 to 1880 in England and France. William Gull, in a paper entitled "On a Cretinoid State Supervening in Adult Life in Women," reported to the Clinical Society of London in 1873 five cases. The term "Myxedema" was supplied by W. H. Ord in 1878. In France, the disease did not escape Charcot's (*a*) shrewd discernment, who described it in 1879 under the term "Cachexie Pachydermique." Myxedema was thought to be confined to females until Savage reported a male case in 1880.

Next ensued the period of etiologic connection of the disease with the thyroid. Madden, in 1880, noted the regular occurrence of thyroid atrophy in myxedema though the significance of this finding escaped him. T. Kocher (*a*) called attention as early as 1874 to the effects of total stru-

mectomy but it was not until April, 1883, that his classical account of *Cachexia Thyropriva* in thirty cases appeared. A little later in the same year, J. L. Reverdin recognized thyroidectomy as the etiologic factor of surgical myxedema. Crotti has made a careful analysis of the Kocher-Reverdin controversy which then ensued, and which chiefly served to bring a thorough understanding of myxedema to the cognizance of the medical world.

Following the discovery of the cause of myxedema, came the therapeutic attempts of Sir Victor Horsley (*f*) and George Murray (*a*) in England which led to the complete demonstration of the efficacy of thyroid feeding in myxedema and cretinism. Hofmeister, Lanz, Vassale and Generali, Pineles and Erdheim (*b*) studied experimental athyrosis with important contributions. To Pineles we are indebted for the recognition of thyroaplasia in man; to Maresch for the first clear differentiation of hypothyroidism from parathyroid disease.

With regard to the metabolism of hypothyroidism, Magnus-Levy in 1897 made the remarkable discovery of the great depression of the same which has since been confirmed by various workers.

Great strides in the knowledge of the thyroid gland have been taken in the decennium 1910-1920 in the United States. For the invention of the respiration apparatus clinically applicable to studying thyroid disease, scientific medicine owes much to Francis E. Benedict and Thorne Carpenter. Elucidation of the problem of diagnosis and treatment of hypothyroidism, with the aid of basal metabolic studies, has been aided by E. DuBois, J. H. Means and J. C. Aub (*b*), H. Plummer and others. To E. C. Kendall belongs the high credit of first isolating in pure form, chemically identifying and synthesizing *thyroxin,* the thyroid hormone; and in conjunction with H. Plummer, applying this compound to the clinical treatment of hypothyroidism.

Definition and Nomenclature

The present chapter deals with morbid conditions caused by decrease or loss of thyroid function as distinguished from *Thyrotoxicosis* (so-called Hyperthyroidism and Exophthalmic Goiter) and *Dysthyroidism.*

Our present want of fundamental knowledge of many thyroid problems unfortunately invites criticism of any possible classification of thyroid diseases. Thus certain authorities argue on just grounds that Thyrotoxicosis is likewise accompanied by loss of normal thyroid function as well as by well-known toxic symptoms. Doubtless also the state of Dysthyroidism may be truly regarded as due, at least in part, to defective thyroid function. For purposes of description, however, the classification adopted in the present work seems advisable. Accordingly, the subject of

Hypothyroidism as here described may be said to include all conditions due to defective thyroid function unaccompanied by the toxic symptoms (tachycardia, exophthalmus, etc.) which also distinguish Graves' disease as well as *Dysthyroidism*, the clinical combination of thyrotoxic and hypothyroid symptoms. Dysthyroidism is treated in a previous section.

Hypothyroidism in its various sporadically occurring forms may further be separated, if uncertainly at best, from the endemically occurring *Cretinic Degeneration* described in the succeeding chapter. The latter condition may at any time exhibit itself in clinical forms identical with hypothyroidism as usually encountered, and has thus given rise to the synonym *Endemic Cretinism*. Certain peculiar characteristics render a separation from hypothyroidism advisable, so the term *Cretinic Degeneration* (Falta) is preferred.

As all clinical types of hypothyroidism described in the present chapter have a common etiology—defective or absent thyroid function—it seems inadvisable to perpetuate the confusion of the past by continuing to recognize the overabundance of synonyms still in use.

In this connection, the term *goiter* may first be discussed. The word goiter simply refers to a state of hypertrophy of the thyroid gland. It may be a prominent symptom of Thyrotoxicosis (Graves' disease). As the first reaction to injury or failing function of this organ from whatsoever cause, goiter may occur as a symptom of hypothyroidism. For this reason so-called "simple goiter" is treated in this section. Again, certain goiters such as that of pregnancy may be regarded as very probably physiologic. Difficulty has, however, arisen in regarding goiter as a separate clinical entity, as has unfortunately been done in most older and some of the latest text-books.

The separation of the subject endemic goiter from endemic cretinism by some authors seems, on the grounds just mentioned, inadvisable though it is true that goiter may be the only striking symptom exhibited in some communities suffering from the cretinic degeneration.

For similar reasons "congenital goiter" is not separated as a topic in this work from other symptoms of hypothyroidism. This viewpoint has been adopted as McCarrison has succeeded in producing experimentally congenital goiters accompanied by other unmistakable general organic changes due to defective thyroid function. The term "toxic goiter" is at times loosely used as a synonym for thyrotoxicosis. The term toxic goiter is unfortunate as it may indicate both cause and effect, a goiter causing toxic symptoms or a goiter produced by an existing toxemia.

A number of writers on the thyroid gland have adopted the terms "Athyreosis" and "Hypothyrosis" (Pineles) as a nosological classification. Although the proof that athyroid individuals may exist is important, still it seems ill advised to thus overemphasize this condition in view of the fact that there are only about fifteen reliable cases of athyreosis on record

and these difficultly distinguishable clinically from other cretins. These cases are therefore described by us under the general clinical title Hypothyroidism.

The term *Cretin,* signifying a small hypothyroid individual, is so firmly established in medical minds of many countries that an attempt to relegate this appellation to disusage would be most inadvisable. The word may be derived from the Latin *creta,* "chalk," or French *cretien,* "innocent," but more likely originated from the Rhaeto-Romanic *cret, cretin,* "dwarf," "little" (Royan). Some slight confusion has, however, arisen from the term "endemic cretinism" which is not general enough to include, as it should, the various manifestations of this degenerative disease. On the whole, however, it seems advisable to retain the term cretin or cretinism as clinically descriptive of the typical dwarfed hypothyroid case but without further significance.

The term "Myxedema" (Ord, 1878) is usually applied as synonymous with severe hypothyroidism in adults and refers especially to the peculiar thickened cutaneous areas. It is therefore only descriptive of the general symptomatology through force of usage. It seems, however, worth while to continue this term as comprehending the classical manifestations of hypothyroidism in adults. There seems little excuse, however, for such terms as *infantile myxedema, juvenile myxedema,* etc. Strictly speaking, myxedema is but a single symptom of hypothyroidism.

Other appellations for hypothyroidism are the French *"cretinisme," "cachexie pachydermique,"* German *"kretinismus,"* Italian and Spanish *"cretinismo,"* Latin *"cachexia strumipriva* and *thyreopriva."*

In the present treatise the medical condition resulting from loss of thyroid function is described under the single heading "Hypothyroidism" as no really significant distinction can be logically drawn between so-called cretinism in children and adult myxedema. Certainly age is no criterion as adult and even senile cretins are known. This conception will be developed in the clinical section where it will be emphasized how goiter, cretinism, myxedema and, indeed, all pathological changes due to loss of thyroid function may merge into each other.

Geographical Distribution

Hypothyroidism may occur among all races and in all countries, though negroes and Chinese are rarely affected. Cases have been more frequently encountered in cold climates. This may possibly be due to the increased caloric requirement in cold weather which is largely controlled by the thyroid. The especial prevalence of the disease in England, France and Germany and other Northern European countries, as reported by many writers, may be partly accounted for by the concentration of

advanced medical knowledge in those countries where this disease was earliest recognized and studied. Certain it is, however, that typical sporadic cretinism and myxedema are less frequently found in America where C. P. Howard, in 1905, collected but a hundred *myxedema* cases from the literature. It is interesting that at least one hundred cases have been reported in California by H. C. Moffitt, the writer, and others. Many of these cases had migrated to this mild climate on account of their great sensitiveness to the cold.

The relation of the distribution of sporadic hypothyroidism to the endemic cretinic degeneration is of interest. Myxedema is certainly no more prevalent in such endemic areas than elsewhere. At times it is less common. As sporadic cretins in such localities are usually confused with the endemic disease, it is difficult to form conclusions in this respect.

Etiology

Heredity and Familial Occurrence.—The marked hereditary tendency of hypothyroidism, though long recognized, has scarcely been sufficiently emphasized. On account of the sterility frequently accompanying severe hypothyroidism, such cases are rarely met. Exceptions do occur, such as McIlwaine's case. More often the parents of cretins show signs of thyroid disease, goiter, thyrotoxicosis, dysthyroidism or mild myxedema. In thyroaplasia characterized by congenital absence of the thyroid gland, heredity is to be regarded as the exciting cause of the disease. Both typical cretinism and myxedema have been reported among children of the same family, particularly sisters. C. Herrman (*b*) described three sporadic cretins and A. G. Paterson two myxedemic patients of the same parents. In the writer's series is an interesting thyroid family showing hereditary obesity, two sisters being myxedemic, a third weighing 225 pounds at 50 years, then developing exophthalmic goiter. Other members suffered from mental diseases. Barrett's remarkable family had sixty-two members with anomalies ascribable to hypothyroidism. It is probable that, with the recognition of increased numbers of light hypothyroid cases with recent new diagnostic aids such as the basal metabolism, the familial tendency will be more often demonstrated. Heredity probably plays an important predisposing as well as exciting etiological rôle. A study of many cases of hypothyroidism makes it probable that the thyroid tissue of various members of a family may be hereditarily deficient, yet enough being present for all ordinary requirements. However, when undue strain such as many pregnancies, infections, toxemias, etc., occur, sclerotic and atrophic processes ensue in such glands with abnormal rapidity followed by the development of hypothyroidism. Other endocrin glands may be hereditarily deficient in similar fashion.

Age.—No age is exempt from the disease. Congenital thyreoaplastic cases develop cretin symptoms shortly after birth. Older children seem more frequently affected in the sixth to the eighth year. At puberty there is an increased incidence, particularly in females. According to Dock (*c*), myxedema gradually increases in frequency up to the forty-fifth year, then decreases, the average age in woman being thirty-eight years, in men forty-two. The earlier age of onset in women is probably related to the increased strain put upon the thyroid by gestation. In general, it may be said that the most active periods of growth of the individual or the embryo are of chief importance in determining the favorite age of incidence; thus illustrating the importance of the thyroid gland in such vital processes.

Sex.—The female sex is predominately affected in childhood according to Hector MacKenzie (*a*), who collected 292 cases of cretinism from the literature of whom 172 or 60 per cent were females. After puberty the proportion of affected females is much greater, 4:1 (Biedl), 7:1 (Dock (*c*)).

In some instances gestation seems to exert a protecting influence against the outbreak of hypothyroidism in predisposed individuals, through a general endocrin stimulus and resulting thyroid hyperplasia. The disease then develops about the menopause. On the other hand, pregnancy may add an overload on a subfunctionating thyroid gland with resulting symptoms of hypothyroidism. Virgins are by no means exempt from hypothyroidism, however. In a case of the writer's series an elderly hypothyroid primipara, who previous to her pregnancy maintained a normal metabolic rate on 0.4 mgm. thyroxin daily, became again hypothyroid during the later months of gestation, the basal metabolism falling to —20. On increasing the daily dose of thyroxin to 0.8 mgm., the subthyroidism subsided and the metabolic rate rose to normal.

Environment.—The causal relationship of unsanitary surroundings to the development of goiter and endemic cretinism has long been recognized. It may, therefore, be expected that sporadic hypothyroidism arises from similar momenta. Clinically, sporadic cretinism is seemingly met with more frequently among the lower orders of society, where probably a combination of etiological factors such as overwork on improper or defective food supply, therefore general nutrition, alcohol, neglected infections, abnormal sexual activity and many pregnancies predispose to hypothyroidism in the offspring.

Infectious Origin.—Major R. McCarrison of the Indian Medical Service has made very valuable experimental contributions on the etiology of goiter and cretinism (see his monograph, bibliography). As his results in these regards are especially pertinent to the Cretinic Degeneration they will here be merely alluded to. McCarrison firmly adheres to the infectious origin of goiter and cretinism in both their sporadic and endemic expressions, believing them frequently due to an infectious intestinal

toxemia induced in turn through an unsanitay environment. Should this viewpoint become general, we could possibly ascribe etiologic significance to enteritis and other gastrointestinal diseases in the production of sporadic hypothyroidism in children and adults.

The rôle played by infectious diseases in the etiology of hypothyroidism is probably greater than generally supposed but is difficult to demonstrate as the thyroid injury sustained may exhibit itself clinically only many months or years afterwards. Should the thyroid be hereditarily subfunctional or be undergoing additional strain as during pregnancy, the intercurrence of an infectious disease is more liable to lead to hypothyroidism. A number of recent clinical and pathological observations have indicated the considerable part played by infections in the etiology of hypothyroidism. Among such diseases are usually included those of children, measles, mumps, whooping-cough, scarlet fever and diphtheria. Archard's case quoted by Crotti developed a myxedematous condition, in a child of ten years of age following measles. This condition persisted until patient's death forty-two years later when autopsy showed complete absence of the thyroid gland. Nearly all ordinary infectious diseases of adults have been said to have been followed by hypothyroidism. They need not be enumerated. Typhoid fever seems but rarely followed by myxedema. McCarrison, however, suggests that the obesity ensuing after an attack of typhoid fever may be thyrogenic. A few cases have succeeded the recent influenza epidemic of 1918 (A. Lopez, etc.). Tuberculosis is not an important causal agent. The thyroid is directly affected only in the general miliary form. Syphilis has rarely been demonstrated as an etiological factor (Koehler, Pel, Pospelow). Such cases improve on specific treatment.

The chronic intoxications such as gout, lead poisoning, chronic alcoholism and the cachexias are occasionally of importance. LaClerc has recently reported two cases of myxedematus children of alcoholic fathers. Bedson's interesting experiments on the production of thyroid hyperplasia and fibrosis from injections of the bodies of helminth worms substantiate clinical observations of myxedema in hosts of these parasites.

Psychic states of grief, anxiety, mental strain, etc., may precede hypothyroidism, especially in predisposed subjects.

Nutritional factors are probably more important than now recognized. Marine and McCarrison observed both experimentally and clinically hypothyroidism to be more common in the presence of undernutrition. According to Bensley's (*c*) observations, the thyroid in hibernating animals decreases much in size and in colloid. Probably the most important nutritional factor is the presence or absence of iodin in the diet. The factor has been more clearly proven for animals than man. An exclusive meat diet not only sets an added strain upon the thyroid (hypertrophy of the thyroid of opossums on meat ingestion, Bensley (*a*)) but also contains almost no iodin.

Trauma and Surgery.—Mechanical injury to the neck is a very rare cause of myxedema as, if but a small portion of the gland remain intact, it can usually replace the whole as to function.

Surgical removal of the entire thyroid was formerly an important cause of myxedema (*cachexia strumipriva*), and led to the recognition of the etiological connection of the thyroid with myxedema (Kocher, Reverdin). Experimental thyroidectomy in animals has clearly shown the necessary presence of the thyroid to prevent hypothyroidism in its severest manifestations (Gley, Vassale and Generale, Pineles, Erdheim, Chvostek). A large variety of animals are now known to develop cretinic characteristics after thyroidectomy. Typical instances of cachexia strumipriva in human beings are quite rare at present, since it is recognized that the retinition of a certain amount of thyroid tissue is necessary for normal thyroid function. Occasionally, however, the remaining portion of the gland atrophies with resulting complete myxedema. More often only mild hypothyroidism develops if overmuch of the gland has been removed. Certain old operated cases exhibit a unique mixture of thyrotoxic and thyroprivic symptoms and are to be classed under the category of dysthyroidism.

The complete surgical removal of the thyroid in children is followed by cretinism without exception. Most writers quote the classical case, then a child of ten years, from whom the thyroid was extirpated by Sick in 1867. When observed by Bruns eighteen years later, typical cretinism had developed. Similar disastrous results of complete thyroidectomy in childhood were reported by Kocher, Combe, *et al.*

Pathology

The lesions met with in hypothyroidism are local, *i. e.,* in the thyroid gland itself, and general, affecting all organs and tissues. Pathological changes in the thyroid gland invariably accompany hypothyroidism. To quote Th. Kocher, that great student of thyroid disease, "Without lesions or absence of the thyroid no myxedema." Congenital absence of the thyroid, *thyroaplasia,* will first be considered in the text, then the changes in the gland met with in hypothyroidism, followed by a systematic description of organic pathology due to the lack of the thyroid secretion.

Thyroaplasia.—It was not until the beginning of the 20th century that the possibility of congenital absence of the thyroid gland was suggested by Siegert upon clinical data and demonstrated pathologically by Pineles. It was later recognized that the thyroid may be hypoplastic at birth, never attaining normal size and function, also that very rarely one lateral lobe may be missing (see further studies by Erdheim (*b*) and Dieterle (*b*)). Pineles described twelve cases of supposed thyroaplasia based

upon postmortem examination but not upon histological studies. Microscopic examination of the gland has, however, been demonstrated to be insufficient to establish the entire absence of thyroid tissue as rests of the same have been discovered among the anterior cervical tissues embedded in fat or at the base of the tongue.

True thyroaplasia is rare. E. Thomas, in his excellent critical survey of this condition, has collected eleven cases in which serial microscopic sections demonstrated the absence of the thyroid. (Langhans, Kocher, Muratow, Maresch, Peucker, Aschoff, Erdheim, Dieterle, MacCallum and Fabyan, Schilder.) The majority were females. All showed high grade cretinism, none becoming sexually developed. All died early, none reaching maturity. Thomas emphasized the condition of *dystopic hypoplasia* of the thyroid, in which the thyroid gland is absent but its function at least in small degree is maintained by tiny rests of thyroid tissue at the root of the tongue. Five cases were collected (Marchand, Schilder, Lezowa, Roussey, Clunet). Instances confidently reported in the literature as thyroaplasia reaching adult life probably belong to this *dystopic hypoplastic* type. The aberrant thyroid tissue in other cases may be functionally of considerable importance, especially when the thyroid gland in the neck is rudimentary. Thus several writers have observed myxedema to appear after the removal of the tongue tumors. Ungerman and Schilder described individuals showing thyroid tissue only at the base of the tongue. In a number of such instances, small cysts which correspond to the *peribrachial bodies* have been found in the cervical tissues. These collections of cells do not form thyroid tissue.

The systemic effects of thyroaplasia are identical with those of severe cretinism.

The Thyroid Gland in Hypothyroidism.—The thyroid gland may show *hyperplastic processes, i. e.,* goiter or hyperplasia. According to the views developed in the discussion of the pathogenesis of goiter all hyperplasia of the thyroid are to be regarded as due to thyroid insufficiency. The goiters of sporadic hypothyroidism may be simple and small, and when larger they often exhibit cystic and other retrogressive changes. They differ in no essential feature from those of endemic goiter, under which heading this topic will be accordingly treated in detail.

More important in the sporadic expression of hypothyroidism are *atrophic changes* in the thyroid gland. In the case of children developing cretinism after a preliminary period of normality, for example about the seventh year, the question may be raised as to whether or not *complete* atrophy of the gland has occurred. This has indeed been found to have taken place in a number of cases. According to the findings of the English Myxedema Commission, Ponfick and Abrikosoff, the pathological process involved is a very chronic connective tissue overgrowth: the alveoli show reduction in size and number of the cells, and round cell

proliferation which can indeed progress until complete disappearance of all glandular structure has taken place. (von Eiselsberg.) A complete fatty degeneration may ensue (Stilling). Hadden very aptly compares the changes to those of chronic diffuse nephritis and cirrhosis of the liver; Thomas to non-tuberculous Addison's disease. For this resemblance there seems good reason as such organic diseases are probably induced by infections similar to those leading to thyroid atrophy. A difference of opinion exists as to whether the acute thyroiditites observed in infectious fevers can lead to the above mentioned extremely chronic cirrhotic atrophy of this ductless gland. Such degenerative processes do not seem to occur as a direct sequence but one cannot exclude thereby the possibility of cause and latent effect.

The histo-pathological changes of the subfunctioning thyroid of myxedema are carefully described by Marine and Lenhart (*f*) as follows: "The colloid is practically absent. The epithelial cells have lost their regular and uniform columnar type characteristic of the early stage of active hyperplasia and are irregular in size and shape. There is perhaps some piling up of the epithelial cells and desquamation of the partially degenerated cells. The nuclei are in general large, often hyperchromatic and irregular in size and outline. Nuclear figures are still observed, but the new formation of cells is not sufficient to offset the cell-death and the follicles become smaller, though still preserving the infoldings of the well-developed hyperplasia. The surrounding fibrous stroma is relatively, perhaps absolutely, increased, as the follicles become smaller from the death of their secreting cells the fibrous bands appear wider, and finally give the appearance of a generalized cirrhosis in which are nests of compressed epithelial cells with or without the outlines of follicles. This interstitial cirrhosis is secondary to and consequent to the death of the epithelial elements. Lymphoid foci are scattered here and there throughout the stroma. This is the simplest picture of the anatomical changes in the thyroid in myxedema, and those occurring in the cretin thyroid are similar. Most cases, either of myxedema or of cretinism, in man do not present so simple an anatomical picture for the reason that other processes as cyst formation, hemorrhage, calcification, adenoma, groups of enlarged follicles filled with desiccated colloid, etc., may all be crowded into the same gland.

"Summing up, then, the type of atrophy supervening on active hyperplasias and clinically associated with myxedema or cretinism is a cell-death due to exhaustion from overwork and malnutrition. The process is simple, but the anatomical changes in such glands, especially in long-standing cases, are often highly complex."

The Systemic Effects of Hypothyroidism.—On account of the control of cellular nutrition, repair, regeneration and growth exercised by the thyroid gland, every tissue and organ in the body is liable to show the

effects of loss of the normal function of this vital hormone producing center. (1) Characteristic of the changes in the young and growing organism are retardation and cessation of growth. We therefore observe tissues and organs in a state of development far earlier than the real age of the hypothyroid individual. (2) In addition is found at times a new pathological tissue peculiar to the disease, which may pervade the skin as well as deeper parts. (3) There is also to be considered the effects of bacterial and other toxins upon an organism deprived of its usual powers of defence, *i. e.*, its normal supply of the thyroid hormone which is essential to maintain the normal resistance against bacterial invasion.

Unfortunately, the pathological researches on hypothyroidism have been chiefly directed, as so often in medicine, at the most striking anomalies, the thyroid itself, the myxedematous tissue, and the skeleton. Few researches have been made on other important organ systems so that our knowledge of their condition in the subthyroid state still remains defective. Many pathological changes such as those of the cutaneous appendages are of symptomological interest and importance. In order, therefore, to avoid later repetition, the present pathological description is chiefly confined to a notation on myxedema and the deep-seated lesions due to defective thyroid function.

Myxedema.—This peculiar substance is found in greatest quantities in the subcutaneous and submucous areas. It may, however, infiltrate various organs and tissues, brain, liver, kidney, muscle, etc. The amount is subject to great variation and may even disappear late in the disease. By the older observers of hypothyroidism, it was regarded as mucin (Ord, Horsley, Halliburton). On closer study, however, it has come rather to be regarded as more complex material. Histologically the connective tissue of the chorion resembles granulation tissue, is markedly hypertrophied, gelatinous and contains increased numbers of nuclei and fibrils. The lymph spaces are distended with a mucoid material which has not been subjected to a thorough modern chemical study. Virchow considered with insufficient reason these changes irritative, resembling granulation tissue. The best supported view, however, regards myxedema as a reversion to an embryonic type of tissue such as is found in the umbilical cord. Little new data have been added in recent years to our knowledge of this peculiar pathological product, which urgently requires restudy with the aid of modern chemical technique.

Nervous System.—The central nervous system suffers severely. The brain in thyroaplasia may show defective convolution and all parts of the central, peripheral and autonomic nervous systems exhibit the signs of retarded and deficient development. This condition is accompanied by degenerative changes which, according to Edmund's (*c*) experiments in animals and Mott's clinical observations, consist in a general chromatolysis, especially marked in the vagal and glossopharyngeal nuclei.

Experimental studies have emphasized the delay in regenerative processes taking place in the peripheral neurons after thyroidectomy (Walter (*a*), Marinesco and Minea). Myxedematous infiltration in and around the nerves may aid in causing functional deficiencies.

Few observations have been made on the pathological changes in the organs of special sense. With regard to the auditory apparatus, Siebenmann found in thyroaplasia a normal condition so far as anatomy goes. There is no question, however, as to the dullness of hearing in myxedema and cretinism and its relief by thyroid therapy; von Wagner believed that myxedematous swellings of tympanum, etc., were present, but Denker was unable to confirm this in careful animal experiments. We must therefore accept cortical deafness or an extremely high grade of sound forgetfulness as the chief auditory disturbance present.

Cardiovascular System.—In certain cases of hypothyroidism there is encountered a general hypoplasia of heart and vessels. The heart muscle is severely affected. Cardiac enlargement with the clinical signs of myocardial degeneration are not uncommon at an early age in cretinism and myxedema. On account of the lowered resistance, valvular disease is rather often met with. For further allusion to the forms of goiter heart see under Cretinic Degeneration. An interesting illustration of degenerative processes which are hastened by a deficient supply of thyroxin to the tissues is the early appearance of arteriosclerosis in hypothyroid subjects. It is surprising how frequently this condition is discovered if sought for. The pathologic changes are those usual in arteriosclerosis from other causes, *i. e.,* atheroma and calcareous deposits. The consequently increased permeability of the vessels walls may possibly account in part for the true edema which, in distinction to myxedema, is sometimes present in the lower limbs of cretins. The pathological changes in the blood are described in the clinical section. The blood pressure is usually low.

Gastro-Intestinal System.—The lingual lesions include hypertrophy of the papillae and mucous membrane, as well as an increase in the interstitial tissue which may not be myxedematous.

The gastro-intestinal tract suffers in a trifold manner. Weakness of the muscularis coat produces gastric and intestinal atony to which the subfunctioning nerve supply, itself in a deficient state of nutrition, contributes. Thirdly, the digestive glands fail to supply properly elaborated secretions for the same reason, and on account of the swelling of the lymphoid tissue. The liver is at times enlarged, infiltrated and congested. Due to the swelling of the bile ducts and the slow flow of bile, gall stones are commonly found according to Hertoghe, who also considers the sallow complexion of the myxedematous subject due in part to biliary absorption. The antitoxic properties of the liver are also interfered with.

The Osseous System.—The osseous system in hypothyroidism, especially cretinism, is the seat of early, important and extensive changes. The

growth anomalies in cretinism have been well delineated by E. Wieland and F. Siegert.

Dwarfism in athyrosis is pronounced. Growth in other less affected hypothyroid individuals is stunted in direct ratio to the amount of functionating thyroid tissue remaining. Even when the other stigmata of the subthyroid condition are very slightly marked, complete cessation of development may occur. On the other hand it is surprising to find adult subjects with hypothyroid disease dating from their early life but with large robust frames of normal height, and yet showing severe signs and symptoms of the disease. It is well in such instances to remember the influence of the pituitary and probably still other endocrin organs upon growth.

In spite of statements in the literature to the contrary, it is probable that the delayed ossification changes may set in at or before birth, the reason being that young infants are seldom carefully examined röntgenologically. This seems likely from the knowledge gained in hypothyroid experiments in animals in which young have been born with pronounced delay in the degree of development of the osseous system usual at birth. Thereafter the youngest case carefully studied seems that of Dieterle (*c*), who described a four months old case of athyrosis with the skeletal development of a newly born baby.

Some of the severest cases of dwarfism known were formerly found among cretins. Thus Telford-Smith's cases measured 30 inches in height at the 16th year. Curling's but 26 inches at the 20th year. The general nature of the bony changes include retardation of ossification and epiphyseal union, osteoporosis, osteosclerosis and marrow changes. The growth retardation is usually reported as proportional, in carefully examined cases such as those of Bourneville (*a*) and von Maresch. Clinical observation, however, certainly suggests that the extremities are more often affected than the trunk. The bones are of normal outline when once formed but the lower extremity is occasionally slightly bowed from defective ossification. Often the bones are apparently normal röntgenologically, except that the appearance of the epiphyses and other distinguishing characteristics are those of an age much younger than that of the subthyroid individual under observation. There is no ground for confusing hypothyroid osseous lesions with rachitic skeletal changes, into which error certain of the older writers, even Virchow, have fallen.

The delay in growth in cretinism is brought about by the late appearance of the bone nuclei and extremely slow ossification of centers already laid down. The epiphyses may be absent many years after they are due to appear and their closure with the shafts of the long bones be indefinitely delayed. It has been demonstrated that this phenomenon is one of the earliest and most constant in hypothyroidism. Even mild cases clinically may show very remarkable delay in bone development which is retarded

even more than the height and size of the body (Argutinsky). Open epiphyseal junctions may persist quite late in life in untreated sporadic cretins. Periosteal as well as endochondral bone formation may be greatly reduced and delayed. The long bone shafts may be the seat of osteoporotic and sclerotic changes, the marrow cavity is usually small, the periosteum thin.

The skull is likewise affected. It is larger proportionally than the rest of the skeleton though not reaching normal size. The cranial bones are thin, poorly ossified and osteoporotic mottling is sometimes evident röntgenologically. Occasionally thickening and sclerosis may be present. Resultingly incomplete closure of the fontanelles is very common. This may persist to adult age. In Bourneville's case the great fontanelle remained open till the twentieth year and never completely ossified. In the writer's series, a twenty-three year old cretin exhibited a saucer-like tender depression in the skull, the site of the great fontanelle, which was, however, closed with an osseous plate. The facial region and *basis cranii* remain especially underdeveloped, giving rise to the protuberant forehead and small features of the cretin.

The *microscopic appearance* of the cretin's long bones is regarded by Dieterle, F. Siegert, *et al.*, as characteristic. The cartilage proliferation zone of the epiphyses is decreased in thickness. The ground substance is augmented in amount. The cartilage cells appear in fewer numbers. The normally regular epiphyseal line of ossification is broken by ingrowths of the marrow substance and is demarcated from the diaphyses by densely laminated cross partitions of bone. This peculiar osseous formation is laid down when growth ceases as a final expression of the proliferating activities of the marrow cells and is regarded as especially characteristic of cretinism. The osteosclerotic and osteoporotic processes show no unusual features. The marrow undergoes degenerative changes.

The *muscles* are infiltrated with mucoid material and may show cloudy swelling, fatty degeneration. The effete substances arising in their metabolism tend to accumulate in the body. The pathologic changes probably come on very early as muscular weakness is one of the earliest signs of hypothyroidism.

The *genito-urinary system* exhibits the usual picture of underdevelopment and degenerative changes, generally characteristic of hypothyroidism. The kidneys are often small in size in young subjects. Histologic studies have been rarely reported, but from the frequency with which albuminuria, cylinduria and even nephritis are known to occur their probable degenerative nature may be readily surmised.

The *genitalia* are hypoplastic and functionally deficient.

Lesions in Other Endocrin Glands.—Other ductless glands may show degenerative changes precisely as do all other tissues and organs of the body for it is likely that the nutritive processes of the endocrin organs

themselves depend on a normal supply of the thyroid hormone. Again these degenerative changes may be due to the same noxus which determined the atrophy of the thyroid. At times the lesions observed are hypertrophic in nature and have been regarded as compensating for the loss of thyroid function. They may, however, be ascribed as well to an irritative toxic reaction such as caused the original thyroid hyperplasia.

A B C

Fig. 1. Sporadic cretinism with acromegaly. (N. W. Janney, original observation.)

The *parathyroid glands* may undergo fibrosis and atrophy of the glandular cells (Victor Horsley (*i*), Forsyth (*b*)). Vesical and colloid formation have been reported by Forsyth and Kojima.

The *pituitary* regularly hypertrophies in animals after thyroidectomy and sometimes in myxedema (various observers). Mott noted that the *pars nervosa* was encroached upon by overgrowth of the *pars intermedia* in hypothyroidism of the psychic type. Schönemann, however, quoted by Crotti, reported that of 112 cases of goiter the hypophysis was atrophied

in proportion to the degenerative changes found in the thyroid. The accompanying illustration (Fig. 1, A, B and C) shows an unusual case of the writer's, acromegaly combined with cretinism.

The thymus has likewise been reported as hypertrophied in hypothyroidism by some authors, by others (Pineles and B. Kasser) sclerotic with absence of lymphocytes and Hassall's corpuscles.

Metabolism

The *Gaseous Metabolism in Cretinism* and *Myxedema* was first investigated by A. Magnus-Levy (*a*) in 1895. He discovered the characteristic reduction in the metabolic rate and noted that the gaseous exchange rose again to normal on suitable therapy. For a long period clinical applications of this important observation failed to be made until the recent respiratory studies of the Americans, E. du Bois, H. Plummer, J. C. Means and J. H. Aub, which have led to the general application of this method. The basal metabolic rate in cretinism and myxedema varies with the severity of the cases and is depressed to as low a level as 40 per cent to 50 per cent in the severest instances. The reduction of the rate is a very constant phenomenon in untreated cases.

Accompanying the general retardation of chemical changes in the organism, urine is usually excreted in less amount and the total solids are reduced. The total nitrogen output of the urine on a mixed diet is usually lowered as the hypothyroid individual usually fails to ingest as much food as normally. Recent studies by the writer and co-workers have, however, shown that the cretin is unable to retain as large amounts of nitrogen as sound individuals under like conditions.

With regard to the metabolic derivatives of protein, contradictory statements are the rule in the older literature. These are due in large degree to faulty analytical technique and to the fact that thyroidectomy affects the mature organism less than it does that of the young. According to Pari and the writer's experiments (*c*), protein destruction takes place at the normal rate in spite of Magnus-Levy's statements to the contrary. Urea and ammonia are excreted in normal proportion to the total nitrogen and the uric acid is decreased (Janney & Isaacson). The metabolism of calcium is much decreased (Hougardy and Langstein).

Creatinin excretion may be slightly decreased or unchanged. The abnormal presence of creatin has been reported by McCrudden, Greenwald and ourselves. These metabolic findings are in general accord with those of other endocrinopathies of a deficiency type so far as investigated. For the effect of thyroid therapy on metabolism, see section Treatment.

Carbohydrate Metabolism is influenced normally to a considerable extent by the thyroid. Failure of normal thyroid function has been found

both experimentally and chemically to lead to increased alimentary tolerance for glucose (Knopfelmacher, McCurdy, Van Noorden (*d*)). The contradictory results obtained by R. Hirsch are subject to other explanation. Gordon noted a tendency of the sugar tolerance of myxedemics to return to normal on thyroid medication. Recently, hypoglycemia has been reported in cretinism, myxedema and in thyroidectomized animals (Geyelin, Janney & Isaacson (*b*)). Experimentally we were able to demonstrate a distinct hypoglycemia and a delayed return of the blood sugar level to normal on feeding glucose to thyroidless dogs. Rarely glycosuria has been reported in hypothyroidism (Van Noorden (*a*)).

The Fat Metabolism.—Like many other endocrin dystrophies, hypothyroidism is accompanied by a tendency to obesity of endogenous nature. This manifestation of disturbed metabolism comes on early and is persistent. Inasmuch as loss of fat which occurs on proper thyroid medication is accompanied by a return of the sugar tolerance to normal limits, thyroid adiposity would seem related to the aberrant carbohydrate metabolism in some manner as yet not fully understood

Statements in the literature in explanation of the metabolic phenomena observed in hypothyroidism are vague and meager. Magnus-Levy's (*f*) attempts to account for the lowered gaseous exchange of hypothyroidism by delayed alimentary absorption of food have, as is noted above, been proven erroneous. The lower nitrogen excretion has been accounted for as due to "lack of the stimulatory effect of the thyroid on metabolism." The writer (*b*) has previously called attention to the inadequacy of such an explanation and endeavored to supply the rationale of hypothyroidism, which may be summarized as follows:—"It is now possible to formulate a more definite conception of the metabolism of hypothyroidism if we keep closely in mind that the thyroid gland functions normally to maintain cellular nutrition and growth. In hypothyroidism these processes are inhibited; the gaseous exchange becomes subnormal and the excretion of protein metabolites is diminished. Experiments carried out by the writer and co-workers demonstrated that even greatly increased amounts of food failed to alter this condition, although the food was well absorbed. Nitrogen balance observations on cretins showed that a normal amount of nitrogen could not be retained by the body tissues and therefore was eliminated by the kidneys in relatively increased amounts. The cretin, however, routinely ingests less food than normal, very probably because it cannot be properly assimilated. Therefore the decreased appetite and lowered nitrogen excretion which is commonly observed in this condition. The basal metabolism is probably set at a lower level in order to spare the tissues as much as possible from ordinary fuel and waste processes as the cells cannot be synthetically repaired and replaced by nutritional processes requiring a normal supply of the thyroid hormone. Many examples of such a sparing effect are known in metabolism. The abnormal excretion

of creatin probably takes place due to degenerative processes in muscle due to loss of normal thyroid function. The lowered secretion of endogenous uric acid is probably compensatory in nature inasmuch as a normal quantity of this important nuclear element cannot be synthetized in the subthyroid state. It is probable that normal protoplasmic repair and growth take place to some extent through intermediary products from carbohydrates. The disturbances of carbohydrate metabolism appearing in hypothyroidism may therefore be connected with the failure of normal cellular nutrition. The adiposity of hypothyroidism may very possibly be due to the diversion into fatty tissue, through synthesis, of products of carbohydrate metabolism which normally would at least in part become anabolized into protoplasmic components."

Symptomatology

Diversity of the Symptoms and Signs.—That the thyroid is certainly one of the most important endocrin organs maintaining cellular nutrition has been emphasized by recent advances in knowledge of the chemistry, histology, pathology and physiology of this gland. Injury to its function may lead, therefore, to a very varied symptomatology as all tissues and organs may become involved. One must, therefore, be prepared to encounter a number of apparently unrelated symptoms and signs of very diverse distribution. In cretins, all organ groups may be affected. Many physicians who were students of medicine one to two decades ago are accustomed to regard cretinism and myxedema as the only forms of hypothyroidism to be encountered. At this time, however, only typical hypothyroid cases were usually recognized. The present day situation is, however, materially changing. Refinements of diagnostic technic permit us to detect hypothyroidism in many more instances than formerly. All groups of organs apparently may not be equally affected. For example, the skin and its appendages rarely escape though no demonstrable clinical changes may be observed in the gastrointestinal tract in numerous instances. If we are alive, however, to the manifold possibilities, many more morbid manifestations will be correctly ascribed to hypothyroidism than hitherto.

Relative Frequency of the Clinical Types of Hypothyroidism.—Cases of hypothyroidism fall very roughly into three types, 1. Hypothyroidism in the young, *cretinism,* 2. Hypothyroidism in adults, *myxedema,* 3. Masked hypothyroidism. Although statistics are unobtainable, it is certain that the atypical or masked hypothyroid cases are much more common than cretinism or myxedema in their typical expression. It is very likely that cretins of the sporadic type will gradually become less frequently encountered in countries in which scientific medicine flourishes,

for it is probable that they will be detected before their malady reaches full development. The same holds true for myxedema.

Acuteness and Chronicity of the Symptoms.—Acute myxedema is a medical curiosity. Such, however, appears to have been the unusual case reported by Osler (*c*), which exhibited rapid development of great obesity, swelling of the face and abdomen, followed by diarrhea, bloody stools, tachycardia, collapse and death. Similar cases have been reported by Anders which exhibit a mixture of hypothyroid and thyrotoxicosis symptoms.

Usually hypothyroidism is an eminently chronic disease. The morbid changes develop so slowly and insidiously that at times neither the patient nor his friends and relatives become alive to the situation until some unduly prominent symptom, such as stubborn obesity or weakness, causes medical advice to be sought.

The effect of the loss of thyroid function upon the growing individual is frequently most serious. The thyroid plays a very important rôle in controlling growth and development, a part not secondary to the pituitary. The results, therefore, of even a slight injury to this gland in the young individual are often severe. Retardation of growth is one of the earliest and most important signs of hypothyroidism. In certain very light cases, it would appear to be the only symptom. In the observation of hypothyroidism in children, it becomes then necessary to make very exact studies by observation of weight, measurements of the height and charting the growth curve. The study of the bony changes has already been described in detail in a previous section.

In two instances, the writer has noted in children an abnormal rate of growth preceding the development of hypothyroidism and growth cessation. One child was accustomed to wear clothing two years above his size before becoming subthyroid. No suggestion of pituitary disease was present but these instances may be analogous to the overgrowth of acromegaly before the development of the degenerative period.

In the succeeding clinical description of hypothyroidism, there will first be given the general description of fully developed hypothyroidism in the young (cretinism) and in the adult (myxedema), then will follow the special symptomatology beginning with local manifestations in the thyroid gland itself. It will be observed that simple goiter, sporadically occurring, for pathological reasons already developed, is regarded merely as an early symptom of hypothyroidism rather than as a disease *per se*.

Athyreosis (*Thyroaplasia*).—Well authenticated cases of congenital absence of the thyroid gland are extremely rare and depend on their recognition on the histo-pathologic findings (see Pathology of Hypothyroidism) as little reliance can be put upon palpation (Bircher, Ewald, etc.). About a dozen authenticated cases are on record. Clinically the appearance is that of grave cretinism beginning at or shortly after birth. The

symptoms usually become apparent from the sixth month according to statements in the literature. Kocher has ascribed this retardation to the protecting influence of the mother's milk. There seems, however, much doubt whether this explanation be correct (Erdheim, Siegert, etc.). In the first place, the young infant leads a nearly automatous existence and incipient hypothyroidism could well go unnoticed for some time. Again, hypothyroid cases have been reported by unusually observant clinicians such as Siegert and Henry Koplik in which the symptoms appeared one month to five weeks after birth. A short period of immunity from hypothyroidism does, however, seem to exist. This the writer is inclined to think may be due to the action of a certain amount of maternal thyroid hormone remaining in the tissues of the child after cessation of the fetal circulation. This lasting effect of the active principle of the thyroid has been observed both experimentally and clinically.

It is doubtful whether an athyroid individual ever survives the age of childhood. Most die in infancy or in the earliest years of life. The oldest case appears to be that of MacCallum and Fabyan, a myxedematous female aged 13 at death. She had not learned to stand, and was able to utter only the words "Papa" and "Mamma." There was practically a total failure of body development. The extremely low resistance of all tissues against infection seems to play an important part in the early demise of athyroid children. The cases of longer persistence of life which are occasionally reported are probably to be accounted for by the presence of accessory thyroid tissue which tends to develop at the base of the tongue and elsewhere. The cases of F. Beach and Bourneville (*a*) which lived beyond puberty fall, in all likelihood, into this category. Bourneville's athyreotic had reached the 37th year. Both cases, on microscopic section of the thyroid region, showed no thyroid tissue. In the more painstakingly studied cases such as Marchand's, who lived to adult age, rests of thyroid tissue were discovered demonstrating them to be hypothyroid and not athyroid cretins.

Formerly it was supposed that the symptoms and signs of thyroaplasia were due also to absence of the parathyroid glands. Maresch, however, nicely demonstrated their presence in his well studied case. This is most important for the clear differentiation of thyroid from parathyroid function. The child was a female reaching the eleventh year of life. Growth ceased at about eighteen months, the total height attained being about 2 feet, 8 inches. It is interesting to note that apparently the other ductless glands were normal. Occasionally the hypophysis is reported enlarged in athyroidism. It is probable that thyroaplasia would be less uncommonly reported if more cretins, dying early, were autopsied and the cervical region sectioned microscopically.

Fetal Athyreosis in Animals has been interestingly described by G. Ennis Smith. This disease is very common among swine in Montana and

certain other Western and Northwestern States, also in Canada. It is said to cause the death of 1,000,000 pigs annually. The affected offspring are hairless, exhibit myxedema and soft hoofs, have little resistance, and soon die. The disease is prevented by administration of potassium iodid and sheep thyroids. This condition is most prevalent in the spring months as the food is lowest in iodin during the winter months.

Fig. 2. Typical cretin. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

Fig. 3. The Cretinic Stare. (Courtesy of Drs. Lewellys Barker and H. I. Goldstein.)

Typical Hypothyroidism in the Young.—*Cretinism* (*general description*).—The term cretinism is used to describe the typical development of hypothyroid symptoms in the young whether they appear in athyroid individuals or in those with present but seriously affected thyroid glands. Mental and physical development is at a minimum.

The cretin's appearance is so utterly repulsive and striking that, once seen, it never escapes the memory. In the case of infants, they indeed resemble, as the older writers are fond of stating, the young of the lower animals. They are stupid sucking idiots with squat, fat bodies and swollen

faces. The complexion is pasty or grey. Their low intelligence is shown by their learning to sit, creep, stand and walk at a late age or not at all. Hearing and sight may be defective, speech hoarse and slowly learned, being often restricted to a few expressions of the simplest needs.

The head is usually small and round and covered with scanty brittle hair; the face is pale; the eyelashes and eyebrows scanty or absent. The small eyes glare forth with an angry expression from between the

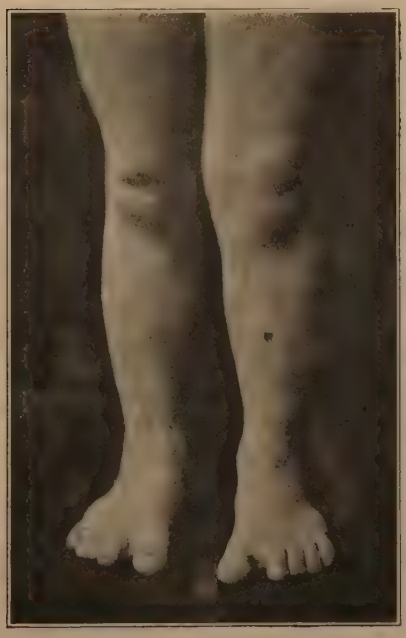


Fig. 4. Cretinic Feet. Note stubbiness and space between great and second toe. Compare Illustration 1. (Courtesy of Drs. Lewellys Barker and H. I. Goldstein.)

Fig. 5. Hypothyroidism in a girl of 10 years. Notice Hertoghe's eyebrow sign, myxedematous swollen eyelids, saddle nose and spade-like hands. (Courtesy of Drs. Lewellys Barker and H. I. Goldstein.)

puffy lids. The ears are large, flaring, and the lobes often fused to the head. Deafness is common. The nose and face is small and retracted, as it were, under the protuberant forehead through the underdevelopment of the base of the skull. The nose is small, of the saddle type, with large open upturned nostrils from which nasal secretion issues. The cheeks may show myxedematous swelling. The malar prominences are quite marked. The mouth is large, lips thick and coarse and druelling saliva. From the open mouth protrudes the large tongue. It is furrowed, tooth-marked, and besprinkled with hypertrophied papillae. The chin is receding and often double through underdevelopment of the mandible and

to myxedema, but this is also due to the stooped carriage of the head, from muscle weakness. The neck may be goitrously deformed.

Such affected children have not enough intelligence for play. If they can walk, they waddle awkwardly about or more often sit listlessly staring in blank fixity. When irritated, they may bellow strangely. When pleased they exhibit that sudden characteristic grin which Garrod has

A B C

Fig. 6. Cretinism with Idiocy, female, aged 23. Note characteristic smile and pot-belly. (N. W. Janney, original observation.)

emphasized. An exaggerated tendency to sleep is frequently present. Their personal habits are uncleanly.

Typical Hypothyroidism in the Adult.—*Myxedema.*—The development of the disease in the adult usually is that of a slowly appearing cachexia. General malaise, weakness, loss of memory and mental irritability or hebetude, drowsiness, lack of concentration are among the first symptoms to appear. Gain of weight rapidly ensues with appearance of myxedematous deposits. The change from health may ensue so gradually

that the patient is scarcely aware of the same. Men holding good positions in life may lose the same because of inefficiency. Women cease to take interest in social life as the veil of illness gradually parts them from the normal activities of their sex. They complain of being no longer liked by their friends and of many vague symptoms which often mislead the physician into carrying out unavailing treatment of various kinds.

As the disease progresses, the facial expression becomes altered. It may assume the peculiar trance-like appearance of the sleep-walker. Im-

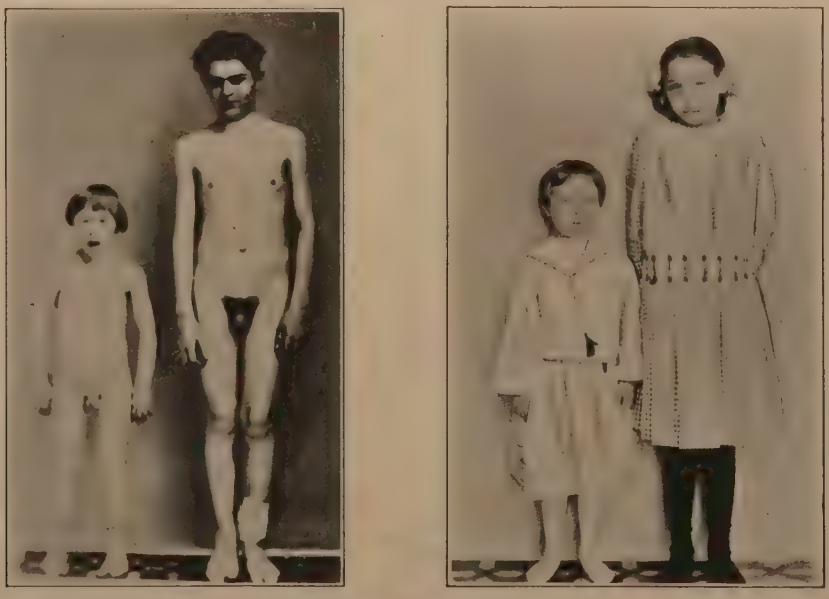


Fig. 7. The stature of cretins compared with normal individuals of the same age. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

mobilization of the eyelids and cheeks through myxedematous swellings are the chief causes of this condition. The face grows pale, the cheeks often flabby, the forehead traversed by wrinkles. The features take on a peculiar coarseness, the lips and ears thicken. At times, weariness or premature senility predominate the impression afforded the observer by sufferers from this strange malady. The various symptoms described in detail below now slowly put in their appearance, the hair of the body is partially lost, the gait and body movements become slow and atactic, the musculature flabby, the digestion impaired.

Symptoms and Signs Referrable to the Thyroid Gland.—The changes in the thyroid gland may be hypertrophic or atrophic nature. Oftentimes, the earliest abnormality, and certainly the most frequent, is a slight symmetrical hypertrophy of the thyroid gland. (For the grounds for regarding thyroid hypertrophy as due to a subfunctioning condition

of the gland, see Pathology of Goiter.) This may be the only demonstrable manifestation of deficient thyroid function. The exposed and prominent position of the thyroid led to an early recognition of this thyroid swelling which received the appellation of "simple" or "benign goiter" when no serious local or general lesions followed its appearance. Due to its frequency in youth, "the goiter of adolescence" is sometimes so designated. It is difficult to exactly differentiate between a swelling of the thyroid of adenomatous nature due to defective thyroid hormone production and a physiological hypertrophy caused by increased need for thyroxin. In the latter category, most "goiters of pregnancy" may fall, though it may be questioned whether such maternal glands are still not functionally deficient

Fig. 8.—Mild myxedema. (Courtesy of Dr. George Dock.)

if they are unable without increase in size, to provide for all the needs of the adult organism including as well those of the growing embryo.

Goiter is much more commonly met with in the endemic cretinic degeneration than in sporadically occurring hypothyroidism. Although it is extremely common in young people, it is much less frequent in well developed cretinism. Occasionally, however, the thyroid may be grossly goitrously degenerated. In Osler's (*a*) series of 60 cases seven had goiters. Cysts are not uncommon in such adenomata. Rarely pressure symptoms may ensue. For clinical symptoms thus caused, see under endemic cretinic degeneration.

In estimating the importance of a simple thyroid swelling unaccompanied by other symptoms, it is well to remember the possibilities. In the vast majority of cases, such goiters either disappear spontaneously or with the aid of medical treatment. They may undergo colloid changes and cease to be of pathologic significance. The bearers of others may, however, develop thyrotoxicosis or Graves' disease, which later on may go over into myxedema. A fourth outcome is possible. The simple adenoma

gradually disappears and later in life, perhaps not until middle age as a result of atrophic changes, the more or less complete clinical picture of hypothyroidism in the adult may develop. The frequency with which

Fig. 9.—Severe myxedema. (Courtesy of Dr. George Dock.)

myxedemea cases on questioning report thyroid swelling in youth, often long forgotten, seems more than coincidence.

The signs of thyroid atrophy are much more often encountered than is goiter, in cases developing a general symptomatology as a result of loss

A B

Fig. 10. The trance-like facial expression of myxedema. (Courtesy of Dr. George Dock.)

of thyroid function. In lean individuals an undue prominence of the larynx with a depression just beneath the cricoid cartilage marking the location of the absent thyroid and its isthmus may be noted as a result

of the atrophy of this endocrin organ. More commonly this appearance is absent and the neck exhibits a normal appearance or even a deceptive fullness due to fat and myxedema.

Palpation as a means of identifying an atrophic thyroid gland may be misleading. First of all it is well to bear in mind that certain glands may be normal in size and texture but yet be functionally deficient. (Ewald *et al.*) Janney and Henderson noted 25 per cent of thyroid glands normal to inspection and palpation in a series of hypothyroid cases. A superficial examination of the anterior cervical region of a hypothyroid subject with the finger tips may suggest a normal thyroid gland due to thickening of the overlying tissues. In order to obtain more accurate palpation, the writer

Fig. 11. The spade-like hands of myxedema. (Courtesy of Dr. George Dock.)

is in the habit of standing facing the patient's back and estimating with closely extended fingers the size of the thyroid by means of a kind of ballottement. It is also to be remembered that senile involution of the thyroid may lead to considerable decrease in size of a normal organ. Although a doubtful diagnosis may be strikingly confirmed at times by thyroid palpation in hypothyroidism, its importance tends to be exaggerated.

General Symptomatology of Hypothyroidism.—The cutaneous system suffers severely. Perhaps this impression, however, may be made upon the clinician on account of the conspicuous location of the skin and its appendages for it is likely that the effects of loss of thyroid function upon the organism are more general than has been generally accepted. The skin is cool due to decreased body temperature, often greyish or a dirty yellow, and shows various signs of degeneration. At times it is thickened. In older cases atrophy may follow, particularly over the shins and extensor surface of the forearm. It may become redundant and wrinkled. Cutaneous dryness is a very frequent symptom. Even severe physical or

mental strain may fail to produce perspiration. The sudorific action of pilocarpin may be absent (Falta). Electric conductivity is decreased. Sebum is excreted in deficient amounts. Nevi and warts may be found. Pigmentation is rare. The writer has observed large, coarse, thickened and pigmented skin areas beset with hairs on the shoulders of adult hypothyroid cases. In light cases merely the texture of the skin may be affected, it becoming rough and dry.

The myxedematous swellings of the skin, mucous membrane and subcutaneous tissues are characteristic of hypothyroidism. On account of

Fig. 12. Supraclavicular fat-padding in hypothyroidism. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

the confusion brought about by using the appellation "myxedema" to adult cases of hypothyroidism, physicians frequently regard such infiltration as a peculiarity of the adult cases. Actually, however, it may be met with in hypothyroid subjects of all ages although it is less common in cretins. Cases of athyreosis are usually swollen with myxedema. Clinically this condition is distinguished by its "solid" texture, an excellent term suggested by Nellis B. Foster. It fails to pit on pressure. Rarely, in very young subjects the whole body may be affected. Usually, however, and regularly in adults the myxedematous infiltration is found confined to the eyelids and brows, and cheeks, lips, nose, neck, supraclavicular fossae, dorsa of hands and feet. Now and then myxedematous swellings appear, at the ankles, or even the back or abdomen.

Thyrogenic Obesity is one of the most early, striking and persistent

signs of the hypothyroid state. It may occur at all ages although it is often extreme about the time of puberty. In distinction to certain other endocrin dystrophies, the fat distribution is usually symmetrical. Sometimes the weight attained is excessive. A case in the writer's series attained the weight of 212 pounds at the twelfth year. Even when growth is practically unaffected, the obesity may be high-grade. Thyrogenic Obesity has been elevated to almost the position of a separate disease by von Noorden (*c*), and much emphasized by many writers including Hertoghe and Ewald. The symptoms are those of obesity, weakness, anemia, apathy, etc. von Noorden especially dwells upon the excellent results of thyroid treatment and intolerance to ordinary reduction methods which greatly weaken such individuals. Such obesity is really only an expression of hypothyroidism of the masked or fruste type of Hertoghe and deserves recognition merely as a prominent symptom of this condition. It is well to remember the possibility of subthyroid function as a cause of obesity.

Fig. 13. Unusual photograph contrasting the generalized obesity of hypothyroidism (right) with the girdle-like obesity of pituitary disease (left). (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

Fig. 14. Hypothyroid baldness. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

All cutaneous appendages are affected in the subthyroid state. The *hair* of the head grows dry, brittle and sparse. It may become prematurely grey. In thyroaplasia, the scalp may be covered merely with lanugo. There is never complete baldness. In young cases, together with the delay in appearance of the secondary sexual characteristics, the *crines pubis* and axillary hair may develop late, be short, frail and small in amount or, in cretins, entirely fail to appear. Hair on the shins, thighs and forearm, etc. may be frequently absent or fall out in adult cases. Alopecia may be marked, particularly over the temples, frontal-band alo-

pecia (Walsh), or by occipital loss of hair, the so-called "cassowary neck" may be suggested. Alopecia areata may be present.

The *eyebrows* may fail to apear in marked cretins or, when present, may be short, sparse and show defective pigment. Frequently the outer third only is affected which may be quite absent, adding to the bizarre appearance of the hypothyroid countenance. This eyebrow sign of Hertoghe, who ably described latent hypothyroidism, is one of the most easily recognized and persistent stigmata of hypothyroidism. Though it may be present in otherwise normal individuals, also in morbid conditions other than thyroid deficiency, its presence should cause such a case to be thoroughly investigated for hypothyroidism. The writer has observed it to be the only certainly detectable physical sign in a patient exhibiting, however, a marked decrease in basal metabolism. The *eyelashes* are short, weak and spaced or even absent in severe cases. This is the cause of the peculiar stare shown by some hypothyroid individuals.

Fig. 15. *Alopecia Areata* of hypothyroid origin. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

The nails suffer in at least 80 per cent of cases. (Janney and Henderson.) The first changes are simply increased softness and brittleness so that patients may complain of their nails breaking or wearing down rapidly to the quick or the finger tips becoming sensitive from lack of protection. In severer cases they may become paper thin or rarely be shed. The lunulae are deficient and white spaces may appear on the matrix. Seaming or cross furrows are occasionally present. At times hyperonychia develops, particularly of the toes. Nail changes are by no means confined to hypothyroidism. The writer has observed all the pathology just enumerated in hypopituitarism and other endocrin diseases. Nail thinning and seaming is met with in thyrotoxicosis. Such signs are, however, in combinations with others extremely important. It is surprising how little attention is generally paid to these "straws which show how the wind is blowing," to use a homely simile.

The mucous membranes may be thickened either *per se* or through underlying myxedematous swellings. Frequently the palatine mucous membrane is pleated into rugae. Vulvar and anal hypertrophies of the mucous membranes may develop in young children. Rectal prolapse may occur.

The *dentition* is rather constantly abnormal. In athyrosis cases, the milk teeth erupt quite late (after the first year). The permanent dentition may quite fail to appear, the teeth remaining submerged in the gums in a rudimentary state of development. In less severe cases, the secondary teeth often come in irregularly and their eruption dates are likewise delayed. The crowns are often poorly facetted with defective enamel. When hypothyroidism appears in adults, the teeth may loosen and fall out. Owing to these factors dental caries, as in all endocrin disorders, is extremely often encountered. The teeth may exhibit a low resistance to mechanical wear and grind off even to the gum's edge. Spacing of the front incisors is emphasized by some. In the writer's experience, it is an inconstant sign of hypothyroidism. The modern management of such cases includes an accurate dental record of the eruption times of the teeth. It is a considerable aid to diagnosis and treatment and should be kept by a skilled dentist.

Various skin diseases are regarded as expressions of hypothyroidism. Such are scleroderma, psoriasis, eczema, ichthyosis, acne vulgaris (Morris), as well as other cutaneous disorders. Occasionally brilliant cures are apparently ascribable to thyroid medication. In these instances, we must distinguish between a direct effect of thyroxin upon the diseased integument and an indirect effect resulting from the general stimulus to metabolism caused by the thyroid hormone. Scleroderma particularly is probably induced in some instances by subthyroid function as atrophic and sclerotic thyroid glands have been found (Hektoen, Laredde and Thomas, etc.). A number of cases of scleroderma exhibit hypothyroid symptoms and yield to thyroid medication. In others, scleroderma is associated with exophthalmic goiter. The relation of the thyroid gland to scleroderma is ably discussed by Osler (*b*), most recently F. Wise.

Central Nervous System.—*Mental abnormalities* are an early and important manifestation of defective thyroid function. In the young, due to failure of brain development, *idiocy* may be complete in the severest cases. Even young hypothyroid infants very early betray mental backwardness. They fail to notice objects about them as do normal babies, and learn to sit, creep, stand and walk at a later age. In this, however, weakness of the locomotor organs plays a part. Mentality tests in older children will often reveal surprising deficiencies even when quite unsuspected by the parents. Occasionally failure of a child to pass examinations at school may be the first suggestion of developing hypothyroidism. Such children may make pitiful efforts to keep up with their classes. Among

backward children who become charges of the state and asylum inmates, close examination revealed 403 in 10,000 to be suffering from demonstrable endocrin dystrophies (Max Schlapp and Paulsen). Of this 403, 79 were hypothyroid cases. It is well to remember that the physical signs of many such cases are so trivial as to be easily overlooked and the mental be very prominent. The psyche of the cretin is classically described as heavy and listless. Though such cases are the most frequent, yet other types of mental disturbances may occur. Certain hypothyroid children are distinguished in the untreated state by their nervousness, crying and screaming on slight provocation. This seems in fact a reaction to the general feeling of malaise experienced by such small patients. It is a significant fact that this nervous irritability frequently yields to proper thyroid treatment. Such nervous hypothyroid children are to be distinguished from the "Nervous Cretinism" of McCarrison, endemic cases exhibiting a spastic paraplegia.

The mentality of older hypothyroid patients is nearly always affected to some degree. Lack of the power of concentration, of memory and will are early symptoms, sometimes the only ones complained of. The disposition may change from the lively to the taciturn, from self-controlled to the irritable. Frequently the patient is well aware of his lowered mentality and uses vain efforts to conceal the same. In severe cases the tendency is usually toward apathy, dullness and depression which many sink deeper into melancholia.

It is a misconception to surmise that subthyroid patients are necessarily incapable of much mental activity. A patient of my series had suffered from marked symptoms of hypothyroidism since boyhood, weighing at puberty over two hundreds pounds and showing marked physical incapacity. His condition remained undiscovered and untreated until middle life. In spite of this, however, this gentleman became prominent in social, civic and literary circles and was regarded among his friends as a man of unusual mental attainments. Close examination, however, elicited a number of peculiar psychic characteristics ascribable to hypothyroidism, mental instability and restlessness, vacillation, and disturbances in the genital sphere. The basal metabolism was minus 30. in the untreated state. The physical signs were unmistakable. A practical cure was obtained by thyroid therapy.

Most cases of pronounced thyroid disease show anomalies in the sexual psyche. These disturbances may or may not accompany physical genital lesions such as impotence. In children, development of the sexual psyche is retarded parallel with the lateness in which puberty appears. In severe cases the sex instinct may fail to appear. Hypothyroid adults present many curious anomalies, often of such vague character that they are with difficulty traceable to their general condition. There may develop mysogyny. Marital relations may suffer and even lead to divorce. Certain

patients masturbate. In one adult case this habit ceased for good two weeks after treatment was instituted. The writer has observed masturbation in even very young subthyroid children.

The relation of the thyroid gland to insanity requires, like so many border-line subjects, a thorough re-investigation with modern methods. It presents a rather inviting field for research. There have, however, already appeared a number of observations which suggest hypothyroidism as the underlying cause in certain grave psychoses. The English Myxedema Commission reported in their series 16 cases of definite psychoses aside from a like number of individuals showing hallucinations and delusions. According to Murray, the hallucinations may be visual and auditory, such as hearing voices, the ringing of bells, photic phenomena or the apparitions of animals. Such delusions and hallucinations clear up when the missing thyroid function is restored through glandular administration. Phillips observed goiter in 12 per cent of patients suffering from psychoses. Seventeen of these patients or 70 per cent were afflicted with manic-depressive insanity or melancholia. The remaining cases were paranoiacs or dementia precox. Certain authors have found thyroid anomalies in the insane to be even more frequent. In one hundred insane cases studied by Kojima the thyroid gland was found to be decreased in size. In 12 per cent of the male and 18 per cent of the female cases hypothyroidism had developed, the gland in each case being small. A type of hypothyroid insanity occurring in women about menopause has been described by Mott together with histopathologic studies. (See Pathology of Hypothyroidism.) Symptoms present are mental confusion, loss of memory, delusions of persecution and hallucinations. Finally a state of dementia intervenes.

An interesting case of myxedematous psychosis with autopsy is recently reported by Uyematsu. In addition to the usual symptoms, drowsiness, vertigo and incoördination were present. Autopsy showed an extremely atrophic fibrous thyroid gland. In the little glandular tissue remaining, lymphatic infiltration had occurred. The case was complicated by ovarian atrophy. The brain and cerebellum showed arteriosclerosis, changes suggesting senility and an edematous condition of the cells. The cerebellum was atrophic, thus explaining the peculiar symptoms. Odin has reported cases with cerebellar symptoms which disappeared under thyroid therapy.

A remarkable family showing a strange mingling of hypothyroid stigmata and neurologic disorders has been recently reported by Barrett. Sixty-one members of six generations were studied. A large number showed dystrophies of nails and hair. In extreme cases merely a lanugo-like covering of the scalp was present. Two individuals had definitely developed hypothyroidism, one patient improving on thyroid medication. The neuropsychiatric abnormalities included four cases of feeblemindedness, one epilepsy, one nocturnal enuresis. Three cases died at an early

age of "marasmus" (cretinism?). It is suggested that the marked frequency in this family of disorders of the skin appendages and nervous system may ultimately be related to their common embryologic origin in the neuroectodermal germ layer.

The *Peripheral Nervous System* suffers likewise. Anæsthesias are infrequent, though myxedemic patients may complain of numbness of fingers, etc., from cutaneous infiltration. Parasthesias, usually itching and burning of the skin, are at times complained of. Aching in the back, shoulders and extremities is not uncommon. Involvement of the motor nerves contributes to the muscular weakness. Rudinger and Falta report a diminished irritability to the electric current in experimental athyrosis, and Erb observed the same condition in myxedema cases. It is very likely that nerve regeneration after injury in severely affected patients would, on investigation, be found to be delayed in hypothyroidism in view of the positive experimental finding on record in this regard. The deep reflexes, though retained, are often weak, due in part to the poor nutrition of the musculature.

The autonomous nerves in thyroid disease have been the subject of various studies by the Vienna School of clinicians in seeking support for their reciprocal hypothesis of endocrin function. Owing to the defective state of nutrition, all drug reactions on the autonomous nerves have an unusually long duration. Included are the miotic reaction of pilocarpin, mydriatic action of atropin, and homoatropin, elimination of vagal function by atropin.

Organs of Special Sense.—The *olfactory sense* may be greatly deficient. Here, as in all the organs of special sense, the question arises as to how much defect be present in the peripheral sense organ or in the cerebral center for the same.

The *eye* is subject to various degenerative changes. In athyrosis near blindness may be caused by imperfect development of the uveal tract. Perhaps this may be the explanation of the lack of light sensitiveness which has been noted in cretins who may pass hours undisturbed by strong sunlight. W. Zentmayer calls attention to the experimental production, by means of thyroidectomy, of keratitis, necrosis of the cornea, blepharitis and conjunctivitis. After strumectomy in man, papilledema and cataract have developed. Risley reports good results in interstitial keratitis, and Bordley in malignant uveitis with thyroid medication. Congenital cataract had been observed by Schioetz in cretinous calves.

Taste is frequently deficient.

Hearing is less often affected than in endemic cretinism, though severely affected sporadic cretins may become very deaf. In myxedema, also, the hearing may grow dull. For the causes of these disturbances, see section Pathology.

Speech is of course lost when hearing is defective. Cretins may be

able to emit but a few unintelligible sounds. All gradations occur from the expression of the simplest wishes to a good command of conversation. The voice is often raucous or nasal due to myxedematous swellings in the larynx and nasal passages. In adults vocal changes occur, as well as the tone scale becoming limited, a monotonous syllabation thus ensuing. It is probable that degenerative fibrillary changes in the vocal cords play here a part. Aside, however, from such local causes, we are confronted by the question of the mutual influence of possible deficiency in higher cerebration (word deafness), as well as defects in motor speech areas.

The Respiratory System.—On account of the defective development of the bones of the face, the nares and nasal passages are often small in young subjects. Myxedematous thickenings of the nasal mucosa may lead to snoring and snuffing. This is regarded by Curtis as the earliest sign of myxedematous infiltration. Chronic rhinitis is frequent. There may be a marked tendency to pick up respiratory infections. Occasionally this alone may bring the patient to a general medical examination and the hypothyroid condition is discovered. Adenoids may obstruct the posterior nares.

Slow respirations are the rule. They may fall to as low as eight a minute. Dyspnea and a sense of oppression are often complained of. These symptoms seemed caused by the possible combination of nasal obstruction with weakened respiratory muscles and involvement of the vagi. Hertoghe calls attention to the similarity of the dyspneic attacks to asthma. True asthma is not infrequently met with in young subjects with defective thyroids. A certain percentage of asthmatics not responding to protein tests, are due to endocrinopathies (G. Piness, G. Selfridge) including hypothyroidism.

Cardiovascular System.—In common with all organs requiring active metabolic processes for performance of their functions, the heart may suffer severely in hypothyroid subjects. Valvular lesions are common. Myocardial degeneration may occur also in young persons. Weak cardiac impulse and the first sound at the apex may call to mind the senile type of myocardial insufficiency. This condition and the trophic degeneration of the cardiac enervation are productive of a sluggish circulation, slow small pulse, and the precordial distress occasionally complained of. For remarks on "goiter heart" see under Cretinic Degeneration.

The blood vessels of the older hypothyroid subjects frequently exhibit arteriosclerosis rarely with atheromatous plaque formation. High blood pressure is unusual, however, in spite of degenerative changes exhibited at times by the renal epithelium. The symptoms of precordial pain, palpitation and tachycardia experienced by certain hypothyroid patients on beginning treatment may, aside from overdosage, be due to the rapid withdrawal of infiltrating substances (Hertoghe) or very possibly to the unusual stimulation of the degenerated cardiac muscle.

The Blood in Hypothyroidism.—The first important studies were carried out by Kocher (*f*) and his pupils in myxedema cases. There is regularly a reduction of the red cells, which is usually of the nature of a mild secondary anemia. The hemoglobin is reduced proportionately. A normal red cell enumeration, which may rarely be found, has been accounted for by a temporarily increased density, i.e., specific gravity of the blood (Schneider). The erythrocytes may be found enlarged, and nucleated cells may appear. Falta reports the presence of myeloblasts. Blood platelets of extraordinary size have been noted. The oxyhemoglobin content is reduced and carbon dioxid increased. The dry residue is decreased. (For literature see Falta's monograph.)

A leucopenia was found in all but 26 cases of 155 cases of myxedema reported by Kocher, the white cell count lying between 3000 and 6000 per cm. as a rule. This was regarded together with a less degree of lymphocytosis as distinguishing obscure myxedema from thyrotoxicosis. This means of differentiation is regarded as valueless by McCarrison, who contends that there is no blood picture typical of either thyrotoxicosis or hypothyroidism. It is, however, certain that a marked relative reduction of the polymorphonuclear cells even to 30 to 40 per cent and an increase of the small lymphocytes is certainly the rule in severe cases of hypothyroidism (Fonio). Concerning the eosinophiles and large mononuclears, a difference of opinion may be noted in the literature. By some writers the eosinophiles are reported increased, not by others who found mononucleosis to be more constant (Falta, Newburgh and Nobel, etc.). The latter condition seems of particular significance. The average leucocytic formula of a series of cases recently studied by the writer and Henderson is polymorphonuclear leucocytes 51.1 per cent, lymphocytes 36.1 per cent, mononuclear leucocytes 3.53 per cent, eosinophiles 0.99 per cent, other elements 1.09 per cent. This blood picture, which may likewise be found in thyrotoxicosis and diseases of other endocrin glands, is regarded as a recession to a fetal type due to degenerative changes in the hematopoietic organs. It is a striking fact that proper thyroid administration causes the leucocytic formula to revert toward the normal. Interruption of treatment causes a return to the former condition. Increased toxicity of the blood serum has also been shown experimentally by Gley. Decreased power to resist bacterial toxins has been reported by Fassin. The oxyhemoglobin has been found reduced by Massin which corresponds to Horsley's observations of the venous appearance of the blood.

The coagulability of the blood is decreased rather constantly (Kocher and Kottman) and should be ascertained in dubious cases. There may be a tendeney to epistaxis and uterine bleeding. Hemorrhagic tendencies in hypothyroid cases have been reported by Hertoghe and others. A very interesting case has recently been described with literature by L. P. Bottaro and J. C. Mussio-Fournier. A girl of eleven years suffered from

menorrhagia lasting twelve days with severe epistaxis. The condition was cured by thyroidin. At the twelfth year the eyebrows began to fall out. When thyroid preparations were omitted, hemorrhagic symptoms of general nature appeared, subconjunctival hemorrhage, epistaxis, hemolysis, epistaxis and purpura. Thyroid therapy arrested the hemorrhages.

The Gastro-Intestinal System.—The mouth tends to be large, the lips coarse and cushioned, the mucous membrane pallid, the hard palate vaulted, the soft, flabby. Rarely the uvula may be edematous. In one case in my series, uvular amputation became necessary. The appetite of cretins has been the subject of comment. Their coarse habits of eating due to feeble-mindedness have, it seems, led to the general impression that they devour abnormally large quantities of food. In carrying out a large number of metabolic experiments, the writer has, however, been brought to accept the fact that the untreated hypothyroid case actually eats less than the normal individual, this because a normal food intake cannot be fully assimilated. (See section Metabolism.) Like other idiots, severe cases of cretinism may deglutate various abnormal materials, even their own excrement. Absence of thirst has been commented upon by various authors. This may be caused both by decreased pulmonary aqueous loss and also by diminution of nitrogenous and other end-products of metabolism requiring urinary dilution for their excretion.

Special studies of the digestive functions seem not to have been made. Certain it is that various vague digestive disturbances are at times complained of and often relieved by thyroid medication. Some cases of myxedema complain of a dragging sensation in the abdomen. Gastroptosis is common. Obstipation due to deficient muscular action of the intestines and abdominal walls is a classical symptom. The bowels move only at long intervals in the untreated state. Even in light hypothyroidism, constipation is a frequent and early symptom. Cecal stasis and chronic colitis are not infrequently met with. Without the aid of thyroid medication, such conditions in subthyroid individuals are particularly refractive to treatment. It should be remembered that a hypofunctional condition of the digestive glands, liver pancreas, gastric and intestinal in common with all organs and tissues is present in hypothyroid individuals. Hepatic enlargement is reported by Argutinsky.

The Genito-Urinary System.—In view of the general reduction in the chemical processes of the body, less urine with decreased amounts of solids is passed in hypothyroid subjects. (See section Metabolism.) The renal epithelium may suffer through the generally disturbed nutrition. Albumin and tube casts are frequently reported in hypothyroid cases though development of progressive nephritides seems, in spite of contrary statements, rarely met with. According to Dock (*c*), albuminuria is present in one-fifth of myxedema cases. Mucin may be found during treat-

ment. In the writer's own experience a youthful member of a hypothyroid family developed, after an infection, a subacute nephritis followed by a persistent albuminuria which cleared up on thyroid treatment. Functional renal studies were negative in this case. A systematic study of renal function in hypothyroidism has not as yet been carried out. Bowen, Byron and Boothby have reported, however, improvement in the functional picture in adult cases after thyroid treatment, a distinguishing feature from ordinary nephritis.

The genitalia frequently suffer severely in young subjects. The parts remain small. Puberty and secondary sex characters may set in late or, in severe cases, fail to appear. Frequently the adult sexual organs, though potent, are much diminished in size. In males, complete impotence is the rule in cretins reaching adult age. Impotence may cease on thyroid treatment to return when the treatment is neglected. This occurred in a patient of Magnus-Levy at the age of 54. The writer can report a similar observation in a man of 55 years. In Herz's case but two weeks were required for a complete restoration of sexual function. Spermatorrhea may occur according to Hertoghe. There seem no recent reports of this anomaly.

The female genitalia may be swollen and the labiae poorly developed, failing to meet in the midline. The uterus may remain tiny and infantile throughout life in the untreated state. Ovulation, menstruation and conception do not occur in the severest cases. Premature menopause may occur in the presence of degenerated and atrophic female genitalia (London and others). Myxedema does not necessarily prevent conception as a number of myxedematous multiparae are cited in the literature. In lighter cases, amenorrhea is frequent, also menorrhagia and dysmenorrhea. In functional menorrhagia and dysmenorrhea, the ovaries and thyroid may be etiologically involved. Certain cases are cured by thyroid medication. For careful studies of these relationships, see E. Novak. Surgical removal of part of the thyroid does not prevent normal pregnancy. In Halsted's (*a*) experiments, the enormously hypertrophied thyroid glands of puppies born under these circumstances seemed to act compensatorily. Attention has already been called to the disturbances in the psychic sexual sphere.

Functional enuresis of childhood of hypothyroid origin was described by Leonard Williams who cured a number of cases by thyroid therapy. It seems regrettable that children are still disciplined for this apparent laxity in their deportment without a proper examination as to the possible presence of a subthyroidal state.

The Locomotor System.—The limbs of cretins are short, stunted, those of myxedematous subjects fat and flabby. The hands and feet are plump and coarsely shaped. The hand is usually described as spade-like (Gull) with short pyramidal fingers usually lying open, due to defective

muscle tone. Shoulders and hips are heavy and thick, the musculature being hidden in fat and myxedematous skin.

The bone changes more properly belong to section on pathology. The changes are those of underdevelopment and imperfect nutrition. As regards general features, scoliosis and lordosis of the vertebrae are frequent. *Genu valgum* and *pes planus* may occur. Mechanical apparatus may be applied to remedy these defects without knowledge of the underlying hypothyroidism. The writer has observed flat-foot so often in subthyroid individuals that he regards it as a not uncommon symptom of this disease. It is aggravated by the obesity of such patients. Hertoghe lays great stress on the crackling sensation (like snow) elicited by palpation of the flexing knee-joint. Perhaps this sign would be observed more often did we seek it. The relation of fractures to thyroid disease is of much interest. On empirical grounds, thyroid substances have been administered and are at times apparently successful in aiding union of ununited fractures. It is likely that defective thyroid function plays quite a part in such cases for the secretion of the thyroid is essential in the regeneration of tissue.

The ligaments are affected as a part of the general state of malnutrition. They tend to become lax, explaining the aching palms and soles of hypothyroid patients. Contractions of the palmar fascia and tendinous shortening have been reported by Levi *et al.* and are said to be relieved by thyroid therapy. Spacing between the great and second toes is common.

The muscles, being the seat of active metabolic processes, suffer particularly severely. They lose their normal contour and tonus, becoming obscured by fat and myxedema. Muscular fatigability and weakness are among the very earliest signs of hypothyroidism. Women complain of the inability to put up their hair. Industrial workers whose occupations require many repetitions of the same movements, such as weaving, become quite early unfit for work. A country woman shown me by Henry Plummer complained of being unable to milk her cow. Stumbling is common. The gait is neatly described by George Dock as "like that of a person stiff from over-exertion." Sudden cramp-like contractions of the muscles may occur, Chvostek's phenomenon may be present, also sudden dropping of the hand and unexpected giving away of the legs. Severely affected cretins cannot stand or walk.

Evidence is beginning to accumulate connecting the chronic myopathies with disorders of the endocrin glands including the thyroid. Thus, progressive muscular dystrophy according to recent studies is probably to be regarded as of endocrin origin. (Timme; Janney, Goodhart and Isaacson; McCrudden and Sargent.) Though various ductless glands may be affected, certain evidence points to the thyroid in certain cases. Several of the writer's series showed, in addition to the myopathy, the bone and metabolism changes characteristic of hypothyroidism, including

underdevelopment of the skull, thinning and rarefaction in the long bones, hypoglycemia, delayed blood glucose curve, creatinuria, etc. Von Werdt's (*b*) case of progressive muscular dystrophy had a colloid struma. Pincherle has recently described a remarkable patient whose condition would certainly suggest hypothyroidism to be the underlying etiological factor at least in this instance. A boy of eleven years exhibited the classical signs of congenital hypothyroidism from early years. Gradually progressive muscular dystrophy of pseudohypertrophic type developed. Thyroid medication caused improvement both of the hypothyroid symptoms and the dystrophic condition of the musculature. Further studies of this myopathy with aid of basal metabolic rate determinations are indicated and may be productive of development of organotherapy in certain types of case.

The Lymphatic System.—Swelling of the lymphatic glands is common in subthyroid children. The occurrence of adenoids has been alluded to. Tonsillar hypertrophy may be extreme. It is surprising how often hypothyroid individuals give a history of unsuccessful tonsillectomies and adenoidectomies in as much as the tonsils, etc., have a tendency to grow again. Before hypothyroidism was recognized, one of my patients gave the history of having undergone three tonsillectomy operations by careful operators but still showed remnants of tonsillar tissue in his throat. Grant Selfridge has called attention to the frequency of an endocrin factor in such cases, in many of which the thyroid is functionally deficient. It is sometimes remarkable that in conjunction with the general improvement of these cases on thyroid treatment the hypertrophied tonsils and adenoids decrease in size. We have here excellent grounds against the indiscriminate practice of nose and throat operations without a general medical revision of the case.

The Temperature.—As a result of the inhibition of all metabolic processes and the circulatory weakness, there is a generally low caloric production. This is evinced by the cool clay-like feel of the skin particularly of the extremities. Hypothyroid individuals frequently complain of the cold and go about in winter bundled in heavy clothing. Nearly all feel better during hot weather. The decrease in perspiration noted in such subjects is probably due, aside from degeneration of the sebaceous follicles, to the lowered requirement for reduction of the body temperature by sweat evaporation.

The body temperatures encountered may be very low, 96° F., or even still more abnormal. The low temperature together with slow pulse and respirations represent some of the most characteristic manifestations of the hypothyroid condition. Fever during attacks of infectious diseases is likely to be lower than in normal individuals.

Hypothyroidism and Senility.—Any careful observer will note the prematurely aged appearance of an advanced case of myxedema, also the

remarkable rejuvenescence which, in certain individuals, occurs on proper thyroid treatment. Perhaps it has been this moment which has caused certain authors, particularly Horsley, to regard senility as a form of hypothyroidism. For this view certain facts speak. The mentality is deficient. The facial expression of the aged sometimes suggests senility. The skin and hair are dry, the latter is lost. Obesity is present. The nervous impulses are slow. The special senses, particularly hearing, are affected and the sexual function weakens. It seems, however, to the writer that in this consideration is perhaps overlooked the general sclerosis of senility which affects all tissues and organs including the ductless glands. It might be more advisable to regard senility as the result of a multiglandular sclerosis in as much as all vital metabolic processes are apparently carried out through their mediation.

Association of Hypothyroidism with other Endocrinopathies may occur. In view of the pathological lesions found at times in the other ductless glands in hypothyroid cases and the probability that the endocrin tissues in common with all organs of the body require a normal supply of thyroxin for nutrition, one may expect symptoms referable to the pituitary glands, etc., to be found in association with hypothyroidism. (See Figs. 1 and 2.) Such clinical syndromes do occur in certain instances. Thus McCarrison draws attention to the prevalence of tetany in Himalayan women who also suffer from hypothyroidism and goiters. Due, however, to the intimate relationship of the ductless glands, these puzzling *Pluriglandular Syndromes* frequently show no predominant affection of any single member of the endocrin system and have therefore received special mention otherwise in the present work.

Diagnosis

The diagnosis of hypothyroidism in its typical expressions, cretinism and myxedema, is obvious on inspection. Perhaps it is that the very grotesqueness of the clinical pictures presented by such patients has fixed the classical type so clearly in the minds of many physicians that the latent or mild cases of subthyroidism are frequently passed by unnoticed. Latent hypothyroidism in children, or *myxedema fruste* in adults, is, however, much more common than the classical clinical syndromes as first emphasized by Hertoghe followed by Kocher, F. Krause, Falta, Leonard Williams and others. Recognition of these atypical cases may be difficult and require most careful observation and consideration. With the hope of aiding the discovery of more of these latent cases, most of which are curable, the following remarks are added.

The family history is important. Questioning may bring out salient points such as history of early or uncontrollable obesity, goiters, protu-

berant eyes or tremor (thyrotoxicosis symptoms), stunted stature, hairlessness, defective nails, etc., as family characteristics. In doubtful cases in children, the parents should be examined on account of the strong familial tendency. In one instance in the writer's experience, the diagnosis became evident in the cases of three children exhibiting retardation of growth through the discovery of marked dysthyroidism in the father.

In considering the diagnosis of hypothyroidism, it is well always to bear in mind that every or any tissue or organ may suffer from a decreased or absent supply of the thyroid hormone. It becomes then particularly important, knowing the possibilities, to note the presence of various slight symptoms and signs occurring coincidentally in diverse situations. Thus in children hypothyroidism is characterized by retardation of growth accompanied by mental and cutaneous abnormalities with obesity. In both children and adults, the psyche, face, teeth, skin and appendages seldom entirely escape. The facial appearance, gait, shape of hands and feet should be observed. The importance of the retardation of pulse, respirations and lowered body temperature is generally underestimated. The writer has been surprised at the regularity of occurrence of these symptoms even in children, making proper allowance for the age.

Laboratory tests have of late become of increasing importance in the detection of hypothyroidism. As these will be treated authoritatively in another section of the present work, no detailed description will be embodied in the present article. Of prime importance is the estimation of the basal metabolism. See articles of DuBois, Means and Aub, Plummer, Janney and Henderson. The basal metabolic rate is decreased in prolonged inanition, diabetes with inanition, and in subfunctional endocrin conditions. Inanition and diabetes can readily be excluded. Among the ductless glandular diseases of subfunctional type, depressing the metabolic rate, hypothyroidism is more frequently met with than any other, also lowers the metabolism to a greater extent. Unfortunately, this test is not now applicable to young children. It is hoped that this lack may be speedily supplied. The blood glucose tolerance test of Hamman and Hirschman as standardized by Janney and Isaacson (*a*) may be regarded as corroborative evidence of the presence of an endocrin disturbance. A blood glucose curve, especially if generally lowered, and with a failure of the blood sugar to return to the normal within two hours' time, are the most important abnormalities met within hypothyroidism.

Variations in the leucocytic formula, particularly lymphocytosis and mononucleosis, though not pathognomonic of hypothyroidism, are found in nearly all cases. Differential blood examinations should be made routinely. The importance of röntgenological studies has been underestimated. Radiograms of the skull and extremities should be made in all doubtful cases, and the developmental stage of the osseous system carefully compared with the normal. (Siegert, Hermann (*a*) and Hess.)

The diagnosis of hypothyroidism should never depend on laboratory tests alone nor, as can now be stated, solely upon the clinical symptoms. Perhaps, however, too great reliance is being placed nowadays on the basal metabolic determinations, the present enthusiasm suggesting that of the period of the introduction of the Wassermann test. If hypothyroidism be present, it will always betray itself to the careful observer by some small clinical signs as indicated in the text. The basal metabolic rate should, however, certainly be estimated whenever possible. If, then, in an obscure case we find some trifling clinical suggestions of hypothyroidism and the laboratory reports a depressed basal metabolism, an abnormal blood glucose curve, lymphocytosis, mononucleosis, retardation of growth of the bone nuclei by röntgen-ray, we can frequently establish the diagnosis.

Much could be written in regard to the therapeutic test which represents the court of last resort in attacking the problem of diagnosis of obscure types of hypothyroidism. As usually employed, the therapeutic test is of only very moderate value. In carrying out this procedure it is not sufficient to give a suspected case a large dose of thyroid for a few days trial. On the contrary, it is frequently necessary to painstakingly study the effect of weeks of small but increasing dosage on the clinical symptoms and metabolic rate before hypothyroidism can be safely excluded or determined to be present. It is well to bear in mind that the required amount of thyroid hormone is an exact quantity which can only be discovered by continued study and observation. No definite rules as to dosage in the therapeutic test can be given. It is the writer's custom to begin with a ½ gr. of standardized thyroid extract or 0.2 mg. thyroxin daily, estimating the basal metabolism at fortnightly intervals. A rise of the rate to normal accompanied by clinical improvement is a strong evidence for hypothyroidism. Large doses of thyroid will elevate, through toxic effect, the basal metabolism in conditions other than hypothyroidism; so caution must be observed.

Differential Diagnosis

Differential Diagnosis in Children.—In the case of infants and young children, errors of diagnosis remain unfortunately rather common, especially as the laboratory aids to diagnosis cannot be carried out or are less reliable. The differential diagnosis of light or incipient cases requires at times a high display of diagnostic acumen. Bearing in mind the enormous importance of an early diagnosis for the future of the individual, every effort should be made to avoid error.

In the presence of a growth anomaly, if the symptoms and signs are chiefly referable to a single organ complex, the case is probably not one of hypothyroidism. Thus a predominance of central and peripheral mor-

bid nervous phenomena should suggest true idiocy, signs limited to bone and cartilage involvement, rickets and chondrodystrophy, etc.

It seems timely to mention, in this period of scientific development of infant feeding, that while morbid conditions of the intestinal tract are receiving as a cause of underdevelopment just attention from pediatricians, the influence of insufficient thyroid function upon normal growth may be overlooked. The same holds true for the food deficiency diseases. Perhaps the wisest course to pursue in difficult cases is to immediately establish an unquestionably proper diet for a given case of failure of development, then only to seek for a possible endocrin factor in the case.

The relative frequency of hypothyroidism of the masked type leads the writer to mention the possible confusion with the *status lymphaticus* or *hypoplasticus*. The status lymphaticus is characterized by hyperplasia of all lymphoid tissues including the thymus, vagotonia at times, cardiac vascular hypoplasia, lymphocytosis, retardation of sexual development and liability to infections and sudden death. Although the Wiesel's and Hedinger's (*a*) studies have connected the status lymphaticus with defective development of the chromaffin tissue of the suprarenal glands, it may be pointed out that many symptoms ascribed to status lymphaticus occur also in hypothyroidism. The lymphatic hyperplasia, though not so marked, is usually present in subthyroid children, also hypoplasia of the cardiovascular and genital tract and at times vagotonic symptoms.

Diagnosis from other Endocrin Dystrophies is not infrequently required in atypical cases. Of such, hypopituitarism may present certain similarities, stunting of growth, obesity, mental dullness, weakness, depression of the basal metabolism.

Fröhlich's syndrome is, however, usually distinguishable through the pituitary type of limbs and hands, the marked developmental delay of the primary and secondary sexual characteristics and the feminine fat distribution usually confined to the parts between the waist and juncture of middle and lower thirds of thigh. Abnormalities in the röntgenogram of the pituitary fossa, accompanied by the symptoms and signs of intracranial pressure are important when present. The ossification is not so markedly retarded as in hypothyroidism. Involvement of the thyroid may, however, be present in hypophyseal conditions and *vice versa*. For example, Josephson's case of congenital thyroid adenoma developed hyperplasia of the pituitary. See also writer's case illustrated in this article. Clinical laboratory tests at present afford, unfortunately, no exact criterion for differential diagnosis between the various endocrinopathies. Indeed, the general experience thus far acquired in this regard suggests a general similitude of results. The basal metabolic rate is decreased both in hypopituitarism and hypothyroidism. If, however, the metabolism is depressed below minus 30 the condition is very probably hypothyroidism.

Eunuchoidism only resembles hypothyroidism in the retardation of the

sex characteristics but the genitalia are usually more hypoplastic when the gonads are affected. The height and length of limb and the fat distribution should readily distinguish it. According to Engelbach and Tierney, the adipose tissue is chiefly confined to the upper femoral region, "the trochanteric fat pads." *True infantilism* (Falta) should cause no confusion with hypothyroidism. Although growth retardation may be marked, yet the symmetrical osseous and limb development and mentality for the age at which normal growth ceased clearly distinguish this condition. *True Nanism* is distinguished by a symmetrical development to the condition of adult life, only differing from normal individuals in the abnormally small size.

Mongolism should cause no doubt in differential diagnosis. A certain superficial resemblance to cretinism is present and has led older writers to the recognition of various differential characteristics. Several hypothyroid manifestations are presented among them retardation of growth, dentition, and of mental development, delayed closure of the fontanelles, protruding tongue, constipation, protuberant abdomen and umbilical hernias. There seems indeed a thyroid factor in certain cases of mongolism as some improvement on thyroid treatment has been reported. The finding of normal thyroids at autopsy (Comby and Bourneville (*b*)) has disposed, however, of the possibility of an actual identity of the two conditions. As differential features may be enumerated the following: The Mongol head is bullet-like and covered with silken hair, the cretin's larger and brachycephalic with sparse dry hair, the Oriental expression of the former contrasting with the bestial type of the latter. Small noses are characteristic of both diseases. The Mongol nose is button-like on a broad base (Kassowitz). The cretin nose is saddled and upturned, showing flaring nostrils. The Mongol tongue is small and pyramidal, the hypothyroid child's over-large, broad and tooth-marked. The Mongol's neck is normal, the cretin's short, fat, double-chinned, with absent thyroid swelling or goiter. The distinguishing hair and skin lesions of the cretin are lacking in the other disease. The hands of both are very distinctive. The Mongol's are gracile and small, the little fingers incurving, the end phalanx being displaced upon the next proximal. The cretin's hands are stubby and plump with short thickened fingers blunt at the tips. The genitalia of the Mongol, though small in males, suffer less developmental delay than in the case of the cretin. Röntgenograms of the bones lack, in the case of the Mongol, the distinctive delay in ossification of hypothyroidism.

Rickets can only cause confusion in atypical cases. The X-ray will show hypertrophic epiphyseal areas and thickened epiphyseal cartilages, irregular lines of ossification as compared to the delayed ossification and straight epiphyseal lines of the cretin. *Chondrodystrophy* is characterized by small stature, short thick bowed extremities. The mind, however,

is normal and the hypothyroid manifestations in the hair, skin and other organs are lacking. The X-ray makes clear the ossification changes peculiar to this disease. *Congenital idiocy* may exhibit amentia resembling advanced cretinism but examination will disclose spasticity, paraplegia or monoplegias, and disturbances of reflexes, the characteristic stigmata of hypothyroidism being absent.

Differential Diagnosis in Adults.—Fully developed myxedema, like cretinism, is unlikely to be confused with other maladies. On account of the pasty complexion, facial swelling particularly when limited to beneath the eyes, the cachexia and anemia, there is a superficial resemblance to *nephritis with edema.* Presence of albumin in the urine, also moderate number of casts, is not conclusive evidence of a renal condition, as such urinary findings are not uncommon in myxedema. Even mental dullness may be present if uremia threatens. A careful history, physical examination and a chemical study of the blood should, however, preclude any error.

Falta mentions the possibility of *persistent erysipeloid* or *indurative syphilitic edema,* also *pachyderma* being mistaken for myxedema. Rarely *cachectic diseases* and *anemias* have been confused with myxedema by superficial observers.

The pains in joints and muscles, heaviness and inhibition of the movements of the extremities resemble *chronic rheumatism,* as Kocher first pointed out. In differentiating between a rheumatoid condition due to inadequate thyroid function and chronic types of articular rheumatism, the therapeutic test is not always of diagnostic service as Rothschild and Levi found a large percentage of the latter cases benefited by thyroid treatment, probably indirectly through increasing resistance.

Gastro-intestinal conditions may be the cause of confusion with subthyroidism. The gastroenterologist is occasionally consulted by hypothyroid individuals complaining of loss of appetite, gastric indigestion, constipation and dragging sensations in abdomen (due to fat, relaxed musculature, and cecal fermentation), these symptoms being so thrust into the foreground that an enthusiastic specialist may fail to detect the latent signs of hypothyroidism. The prompt improvement of the gastro-intestinal symptoms on thyroid therapy in myxedema is a sufficient proof of their thyrogenic origin. A case in my series had been treated for colitis with toxemia for many years. The slow pulse, chilliness, slight myxedemic expression and vague psychic symptoms found to be present suggested hypothyroidism which was confirmed by the additional evidence of mononucleosis, lymphocytosis in the blood formula and a basal metabolism of minus 20. A carefully controlled exhibition of thyroid extract led to a complete recovery of the intestinal function as well.

Psychoses. The mental symptoms may rather frequently be the presenting and may occasionally lead to a wrong diagnosis. The indefiniteness of the subthyroid psychoses in combination with evident signs of hypo-

thyroidism is usually characteristic. A case which came under personal observation had spent many months in a madhouse. Under prolonged thyroid treatment a practical recovery ensued.

The writer has been surprised by the relative frequency with which subthyroid individuals have been diagnosed as cases of neurasthenia. It does not seem to have been sufficiently impressed upon the minds of the profession at large that many of the symptoms of neurasthenia are merely those of hypothyroidism. Thus one may mention the easy mental and physical fatigability, the loss of power of concentration, eye-strain for insufficient cause, the irritability and depression, the itching skin, the paresthesias, the reflex gastric and intestinal disturbances, the vague malaise, also muscle and joint pains. More careful clinical studies with proper diagnostic aids, such as the basal metabolism, will discover more endocrin cases among these discouraging individuals.

The Obesities. It seems scarcely justifiable to ever regard thyrogenic obesity as a disease *per se,* as it is actually but a prominent symptom of decreased thyroid function, i. e., hypothyroidism. Therefore, it would rather be preferable to regard the differentiation of the endocrin obesities in the light of their causal conditions, hypopituitarism, eunuchoidism, etc., to which allusion has already been made.

Adipositas dolorosa (Dercum) deserves special mention. This condition of painful obesity cannot be clearly differentiated in all cases from hypothyroidism, as chronic thyroid lesions, sometimes of inflammatory nature, have been found in the majority of the autopsied cases. Pathological changes in other ductless glands have, however, been observed and opinions as to its etiology are conflicting. Clinically, the psychic changes, general weakness, and obesity suggest hypothyroidism but painful fat nodules and the freedom of the face from myxedema or invasion by the lipomatous overgrowth distinguish this condition rather clearly.

Prognosis

The prognosis of athyroidism in the untreated state is fatal. Few survive the very early years. No authentic case seems to have reached maturity. Death usually ensues from intercurrent disease due to lowered resistance. In general, the prognosis of athyroidism and hypothyroidism depends on efficient treatment with thyroid preparations. As such therapy requires painstaking scientific control, one is scarcely justified in considering thyroid deficiency so readily curable as the older text-books suggest. The age of the patient at the time treatment is begun greatly influences prognosis. If previous to closure of the epiphysis, growth on proper treatment may again be established and a nearly normal organism result.

If treatment be begun at a later period the prognosis is less favorable.

In untreated myxedema the prognosis as to life is fairly good but poor as to mental and physical efficiency. A few cases of spontaneous recovery have been reported. Although the most marvelous cures known to medicine are frequently made in hypothyroidism when treated skillfully, a perfect restoration to physical and mental normality is seldom attained. In children, growth often remains tardy; in adults some of the hypothyroid bodily and psychic changes usually persist.

Social environment affects the prognosis. The poor and ignorant frequently neglect treatment or its proper control and suffer accordingly.

The prognosis of hypothyroidism can certainly be regarded as better since the clinical introduction of basal metabolism studies which permit of a more accurate control of treatment.

Treatment

The therapeutical results obtained in hypothyroidism through the extraneous introduction of thyroid preparations are among the most brilliant and ideal in modern medicine. The rudiments of the science of organo- or opotherapy at present in our possession have been largely elaborated as a result of the stimulus given to endocrin research by the success of thyroid therapy. On account of the practical and historical importance of this discovery, the following is quoted from Geo. R. Murray's (*f*) description of the first use of the thyroid gland in treatment.

"The symptoms of the disease having thus been traced to loss of the thyroid gland, the next advance was in the direction of supplying the deficiency. Schiff had already shown that the usual fatal result of thyroidectomy in the dog could be averted by a preliminary transplantation of another thyroid gland into the abdomen of the animal, and von Eiselsberg proved that the same result could be obtained in the cat, provided the graft was successful. Quite independently, 1890, thyroid grafting was suggested by Sir Victor Horsley as a method of arresting the disease in man. This suggestion was acted upon by several surgeons, especially by Bettencourt and Serrano, who noticed that in their case the operation was immediately followed by improvement, which they attributed to absorption of the juice of the transplanted thyroid gland. This observation appeared to me to be extremely important, as it indicated that the thyroid gland carried on its function by means of an internal secretion. I, therefore, concluded that if this was the case the regular use of the secretion, obtained in the form of an extract of the gland, would remove the symptoms of myxedema, and suggested this line of treatment at a meeting of the Northumberland and Durham Medical Society in February, 1891. In order to test this a glycerin extract of the sheep's thyroid gland was prepared, and injected at intervals beneath the skin so as to ensure its

absorption by the lymphatics in the same manner as the normal secretion is conveyed into the circulation from the healthy gland. The symptoms of myxedema in the first case I treated in this manner rapidly disappeared, thus proving that the thyroid gland is a true internal secretory gland, and that the thyroid extract is a specific remedy for myxedema. The following year it was shown by Howitz, of Copenhagen, and by Dr. Hector Mackenzie and Dr. E. L. Fox, in England, that the same results could be obtained by the simple method of giving thyroid extract or the raw gland itself by the mouth."

The effect of thyroid medication upon the symptoms of hypothyroidism is a general tendency to return to the normal condition. In every tissue and organ, the therapeutic effect may be manifest, so that the result may

Fig. 16. The same myxedema patient before (left) and after (right) thyroid treatment. (Courtesy of Drs. Wm. Engelbach and J. L. Tierney.)

be positively startling in some instances. A decided change for the better, especially in the mentality, may be noticeable within a few days, to be followed in succession by improvement in the rapidly growing tissues such as the skin, and finally in the internal organs, the skeleton and dentition. In children growth and development is again resumed. Sometimes this may be so rapid, according to Hertoghe, that kyphosis and scoliosis may result. Bowing of the legs may be induced at first. The ability to grow depends upon the epiphyses remaining open. Growth is usually difficult to obtain after the twentieth year though it has occurred up to the thirtieth. There is usually very rapid increase in stature at the outset of treatment, four or five inches being at times attained. Later there ensues a gradual return to the normal growth curve. Severe cases of cretinism, no matter how well treated, rarely attain normal size. Although not anatomically, functionally perfect results may be obtained. Thus Hector McKenzie's male cretin began treatment at the eleventh year and at the twenty-fifth had become in every respect a normal individual except for shortness of stature (5 ft. 4 in.).

The face enlarges, the nose and eyes become more prominent, the lips become normal in size, the voice takes on its natural qualities, the pot-belly and abdominal hernia disappear, the limbs grow proportionally—the extremities losing their stubbiness. The muscles harden, the myxedema disappears and the skin grows soft and moist. The normal mentality for the age is regained to a greater or less degree. The gait and bodily movements recover their agility. In course of months or years, a helpless, drooling idiot may become transformed into a healthy beautiful child.

The *skin and its appendages* undergo striking changes on proper treatment. The texture, normal thickness, color, moisture and mobility of this organ are quickly restored. The nails become normal. The hair becomes glossy, properly pigmented and plentiful areas of alopecia may soon be covered with a downy new growth and later with normal hair. Strandberg reports renewed growth of hair in three of nine cases of alopecia areata showing otherwise no thyroid symptoms. G. R. Murray, in *Allbutt's System of Medicine,* has published a remarkable photograph of a bald male myxedemic who three months later is again pictured with a heavy growth of normal hair. McCarrison mentions a tendency of the hair to fall out at the beginning of treatment, to be followed by a thick new growth. Diffused hair sparseness is likewise favorably influenced by treatment. The *dentition* may undergo an astonishing degree of development even when greatly retarded. Thus Kassowitz's twenty-two-month-old cretin was toothless, but sixteen teeth were erupted during the next six months on treatment. Resumption of normal eruption periods of the permanent teeth is one of the certain signs of general improvement.

The *mental improvement* in myxedema on proper thyroid medication is striking. The apathy disappears, the memory and the ability to concentrate return, the normal play of emotion sets in, and the usual mental activities of the individual are resumed. Psychoses of subthyroid origin may disappear completely under treatment. One of the writer's patients eloquently described this great inward change by saying, "I stepped from out the world of shadows and uncertainties into the bright sunlight of vivid human existence, astounded beyond words to think and feel as a normal man again. Each day teems with delightful experiences of a renewed existence."

The *special senses* regain their activity early. Among the most interesting effects is that on speech. Children, who previously could mutter only "Papa" or "Mamma" begin to prattle freely. Normal chattiness replaces the stupid silence of the cretin or myxedemic. Magnus-Levy refers to the appearance of stuttering at the beginning of treatment. The writer has observed slowing of the speech to the normal in the cases of psychoses of the excitable type on a subthyroid basis.

The *secondary* sexual characteristics may, under proper treatment, develop long after the usual age of puberty has been passed. An interest-

ing case reported by Magnus-Levy underwent complete thyroidectomy at the age of fourteen. Sexual development did not appear. At the twenty-eighth year, successful thyroid therapy was begun. At the thirtieth year sexual development began and was completed by the thirty-fifth year. A certain degree of sexual maturity was also obtained in the case of a cretin of forty-five. Menstruation sets in again in the female and males may recover their potency. The *libido sexualis* reappears.

Clinical Control of Treatment.—Certain clinical aids to treatment should be systematically observed and charted in order to obtain the best results. The pulse, temperature and respiration should, if the dose be proper, return to normal in about 10 days' time and remain there. It is doubtful whether it is ever advisable to permit, as did the older clinicians, a *state of toxicity* to develop with nervous excitability, tachycardia, palpitation, tremor, sudoresis and diarrhea. Frequently and even in young subjects a degree of myocardial insufficiency is present in the untreated condition and it is questionable whether more strain should be added to the heart muscle by even permitting tachycardia when it is avoidable. It seems also unnecessary to advise bed rest as did Hertoghe on this account at beginning treatment. A slight acceleration of the pulse rate may be countenanced at the outset but this should not be permitted to persist very long. The writer is accustomed to decrease the dosage should the pulse-rate be found to range 90 or more.

The *reaction to the initial dosage* is of much importance. Statements in the literature are in this regard somewhat conflicting, some authors maintaining that subthyroid individuals are more, others that they are less sensitive than normals to thyroid medication. This confusion has arisen from the following causes: First there is an occasional tendency of subthyroid individuals to react violently to even minimal doses. Thus a case of cretinism, a boy of six years, developed great restlessness, precordial pain, tremor of hands, temperature 102°, with tachycardia to 135 per minute on 1/8 grain of thyroid extract (0.2 per cent iodin) per diem. Some months later the same patient developed a tolerance to 2 gr. thyroid extract daily which had only a therapeutic effect. Most cases of hypothyroidism tolerate from the outset much more thyroid substance than do normals. This is true for both mild and severe expressions of the disease.

Röntgenological examinations of the epiphyses should be made at intervals of about three months in young subjects during treatment and growth changes recorded *ad seriatum*. Such röntgenograms are most instructive.

The *weight curve* is of much importance especially in children. It should be charted at about weekly intervals. At first a preliminary fall of weight may be expected which usually lasts but a few weeks at most. If treatment be efficacious thereafter a steady rise in weight together with improvement of the clinical symptoms should then ensue. This should

equal or, in favorable instances, excel the normal growth curve. In adults the aim of treatment is to reduce the weight to normal and maintain it there. One of the first indications of insufficient dosage in hypothyroidism of adults is a gain of weight. If, as sometimes happens, the affected individual has always been obese, the ideal weight for the sex, height and age may be accepted as a criterion of treatment.

Regular and accurately taken records of the *height* of children are of much importance in determining whether true growth has been resumed. Such estimations are best made at monthly intervals.

The *leucocytic formula* is of some aid to treatment but only of confirmatory nature. The per cent of polymorphonuclear elements tends to rise as the mononucleosis and lymphocytosis subsides. (Falta (*a*), Esser.) The writer has frequently observed the same reaction. The differential count is so readily taken and recorded that it is surprising that this clinical feature has been so often neglected. The secondary anemia rapidly disappears in well treated cases, the hemoglobin and red cell count rising to the normal.

Thyroid Preparations and Dosage.—Since Murray's first success, a variety of thyroid preparations have been used as therapeutic agents. These preparations usually took the form of impure extracts or derivatives of the thyroid, therefore of dubious efficiency. It seems unnecessary to perpetuate remembrance of the same by special mention. With the recent isolation of the thyroid hormone by E. C. Kendall (*f*), there began a new era in thyroid physiology and therapy. A detailed description of the preparation and the chemical properties of thyroxin is not pertinent to the present clinical article and will be found elsewhere in the present work. The thyroid hormone or thyroxin has been demonstrated by Kendall and Plummer to possess practically all the therapeutic effects ascribable to the thyroid gland or any of its preparations. These observations have been corroborated by Janney, Rowntree and co-workers. We are then in final possession of the active principle of the thyroid gland which can be prepared chemically pure, be accurately weighed, measured and prescribed. Thyroxin is now obtainable commercially in doses of 0.2, 0.4, 0.6, 0.8 and 1.0 mgm. The smaller doses are efficacious in mild hypothyroidism, the larger being usually necessary in cretinism or myxedema. It is usually administered by mouth though good results of intravenous injections have been reported. (Kendall, Rowntree.) Overdosage will produce a toxic state of so-called hypothyroidism and even death. (Kendall.) It is remarkable that a latent period of a number of days' duration passes before the effects become evident, also that the therapeutic effect once established tends to persist for a certain time. In view of this fact, it has become the writer's custom to administer but a single daily dose which has practical advantages. If toxic doses are administered, the latent period is much shortened (24-36 hours for animals). The elevating action on

the basal metabolism is so constant that Henry Plummer could estimate that 1 mg. thyroxin increases by 2 per cent the basal metabolism of an adult weighing approximately 150 pounds. Apparently the sole objection to the clinical use of thyroxin is its present expense.

Excellent dried thyroid extracts are now obtainable which contain a known quantity of iodin (usually 0.2 per cent) therefore a fairly constant amount of thyroxin. With the best of such preparations the general experience has been good. Their use is entirely justifiable and their cheapness recommends them for dispensary and poorer practice. The oral dosage ranges from ⅛ gr. in light to 5 or 6 gr. per diem in severe cases. The general tendency is to administer smaller doses than formerly. The correctness of this view has been established by recent studies of the basal metabolism.

Metabolic Control of Treatment.—The modern basal metabolic rate determinations have one of their chief uses in the control of thyroid treatment. Succeeding the preliminary studies by DuBois, Means and Aub, Plummer, Rowntree, Janney and others, this method is in process of general introduction at the present writing (1921). In hypothyroidism, the basal metabolic rate rises promptly on thyroid medication, reaching in a few days to a fortnight the normal when the dosage has been correctly chosen. Aside from the accompanying symptoms of thyrotoxicosis, an overdose of thyroid substance will elevate the gaseous exchange to above the normal. Conversely on insufficient dosage the rate will fail to reach this level. If technically accurate metabolism determinations are made at regular intervals in carrying out the thyroid treatment of hypothyroidism there is no question of their great utility as illustrated by the accompanying charts. (See pp. 434 and 440.) Changes of dosage can frequently be both indicated and very accurately controlled in this manner. Whenever possible such methods should be employed.

In the present period of overenthusiasm following the recent introduction of this method, there seems, however, a tendency to overestimate its value. It is by no means an absolute criterion. Thus several cases of hypothyroidism have been observed by the writer in which thyroid treatment promptly brought the metabolic rate to normal, but in spite of this, the patients remained obese, the mental condition was only imperfectly relieved and the temperature remained below the normal. Attempts at further increase of the dosage led to thyrotoxic symptoms with an increase in the metabolic rate. The writer with Henderson has also reported two interesting cases of hypothyroidism in whom complete hysterectomy had been carried out with the result that it was never possible to elevate the metabolic rate to normal by thyroid medication, without a thyrotoxic outbreak intervening. The probable explanation for this phenomenon is that the reduction of the basal metabolism in such instances is partly due to the absence of ovarian function, inasmuch as Murlin and Bailey have observed

decrease in the basal metabolism experimentally in animals after ovariectomy. It should also be recollected that inanition and various endocrinopathies other than the thyroid depress the gaseous exchange and may in complicated cases, such as the pluriglandular syndromes, render this excellent therapeutic aid somewhat misleading.

The *nitrogen metabolism* has been variously studied in the treatment of hypothyroidism (Magnus-Levy *et al.*). On account of the labor and cumbersomeness of carrying out accurate nitrogen balance observations, this procedure is of little clinical value. There is good experimental evidence, however, for believing that changes in the nitrogen balance accompany thyroid therapy. On several occasions, the writer has found a distinct gain in the amount of nitrogen retained in the body to result from accurately controlled thyroid therapy in hypothyroidism. It is likely, for reasons which cannot be entered into on account of brevity, that a gain in the nitrogen balance regularly accompanies the renewed growth or tissue regeneration caused by the thyroid therapy in subthyroidism. The loss of nitrogen sometimes reported under such conditions is very likely a toxic loss except at the very incipiency of treatment when the "slack" nitrogen of the body and the melting of myxedematous tissue may lead to a preliminary increase in the nitrogen output.

The *blood glucose curve,* though of some utility in the diagnosis of hypothyroidism, is of little value in the treatment as it undergoes oscillations which scarcely permit of definite analysis. There is, however, a general tendency of the blood sugar curve to become elevated during periods of thyroid medication in the case of cretins or myxedemics (Janney).

Dietetic Treatment of Hypothyroidism.—But very few observations in this regard have been reported. In view, however, of the great importance of the thyroid for the regeneration and repair of the body tissues as well as in growth, it is obvious that only a therapeutic effect could be expected from thyroid medication when the patient was on a suitable dietary. Frequently this diet is found to be overrich in protein, and deficient in fats and carbohydrates, on account of efforts on the part of patient or physician to combat the accompanying obesity. The results of an inadvised reduction cure in the presence of hypothyroidism may be serious. The patient, in an already weakened state, may become so depressed and asthenic that many months of judicious thyroid medication and dietetic care may be required for a restoration of health. It is not justifiable to permit a high protein diet as experimentally this has been shown to lay an added burden on the thyroid gland which in hypothyroidism is already weakened in function. From prolonged metabolic studies of the effect of various dietaries in cretinism, the writer has come to the conclusion that a fairly high caloric diet of normal balance as to carbohydrate, protein and fat is the most suitable in hypothyroidism. Such

a regimen seems also to be indicated on *a priori* grounds in order to supply all the tissue "Bausteine" needed for a resumption through aid of thyroxin of normal nutrition and growth processes.

Thyroid Transplantation.—Although thyroid transplantation has been attempted by scores of investigators, not a single permanent result has been reported to the writer's knowledge. The grafted glands may, as did Bircher's early case in 1889, indeed relieve the symptoms of myxedema temporarily but the grafts gradually become absorbed. Every conceivable location in the body has been tried in vain. Considerable experimental research has demonstrated that although autotransplantation may succeed, yet heteroplasty, *i. e.,* the donor being of a different species, or even homotransplantation, *i. e.,* transplantation using two individuals of the same species, fail with regularity. This has been accounted for by Enderlen and Borst and others as due to individual differences in the molecular configuration of the tissue proteins. This seems indeed possible as Emil Fischer's researches have demonstrated the possibility of each individual having protoplasm differing chemically.

Interesting observations on thyroid grafting have been made by Manley and Marine who found that homographs of the thyroid lasted much longer if grafts and hosts were iodinized. One is here reminded of the favorable effect of thyroid substance on tissues growing *in vitro* (Carrel), an unique example of the controlling influence of the thyroid on growth of tissue. Thyroid transplantation must unfortunately still be regarded as in the experimental stage and is not recognized as a clinical therapeutic method at the present time.

Surgical Treatment.—Surgical treatment may become indicated for large, cystic or degenerated goiters, or in the presence of pressure symptoms. Careful judgment should be exercised in advising removal of thyroid tissue in the presence of hypothyroid symptoms as *cachexia strumipriva* may result. The mortality of strumectomy in the hands of skillful operators has been reduced to a minimum. The details of indications for operation and technic are beyond the limitations of the present work.

Illustrative Cases of Hypothyroidism

Hypothyroidism in Children.—*Case No. 1960, boy of 12.*—Mother is myxedemic; had an initial basal metabolism of 19 per cent; was cured by administration of thyroxin. An older brother has a saddle nose and swellings of the under eyelids, but a normal basal metabolism, normal growth, and no other symptoms of hypothyroidism. Patient was regarded as being in perfect health, making no complaints whatsoever; was examined at request of mother. Present weight (October 24, 1919) 84¼ lbs. On questioning, it was found that the boy was a little dull at school

and not very active at play and had failed to grow for past few months only. His disposition was *laissez faire* in type.

Physical examination showed the following:—Apparently very healthy boy; skin dry; no axillary nor pubic hair, genitals undeveloped; hands and feet cold; fingers short, rather stubby; same true of hands and feet; hands and feet slightly cyanotic; no cutaneous atrophy; skeleton symmetrically developed. Hair of head abundant, a little dry; eyebrows very scanty, particularly outer thirds; eyelashes normal; ocular movement normal, pupils dilated; ear-lobes normal; moderate deviation of septum to right; very high arched palate; tongue, no tremor; panniculus normal. Teeth normal in appearance but first pre-molar on either side not erupted.

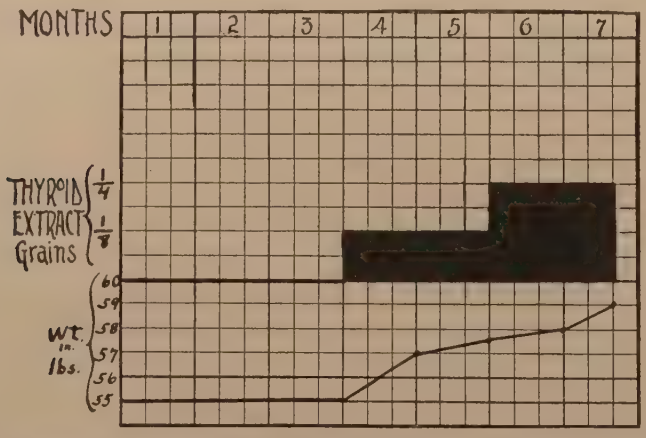


Fig. 17. Masked hypothyroidism; boy of 12 years. Note resumption of growth on thyroid treatment. (From Janney and Henderson, Arch. Int. Med., Vol. xxvi, pp. 297-318, 1920, by permission.)

Thyroid scarcely palpable, apparently some tissue on the right side; isthmus palpable. Lungs normal. Heart normal size. Sounds:—musical systolic murmur, high pitched, heard close to sternum at apex. Abdomen normal in appearance; liver not enlarged; no abnormalities. Reflexes normal. Pulse rhythmic and normal rate. Temperature subnormal. Respiration normal. Initial basal metabolism rate was found to be —27. Glucose tolerance test could not be carried out. The urine is normal; blood count, hemoglobin 88 per cent; leucocytes 11,000, erythrocytes 5,450,000, polymorphonuclear leucocytes 65 per cent, neutrophiles 32.3, mononuclears 1.6, basophiles 0.3, eosinophiles 0.6. Diagnosis, Hypothyroidism of masked type.

The course of the case is well shown by the accompanying figure. It is remarkable inasmuch as a few weeks after thyroid treatment was instituted hyperemic areas were observed developing in the region of the eyebrows. A short time later, the absent two-thirds of the eyebrows began to grow

in on either side. This growth has continued until the eyebrows are at present normally extended. The boy became mentally alert. A very noticeable result of treatment was the very rapid development of his second dentition which had been previously quite retarded. A normal growth curve became reëstablished. The case is extraordinary on account of a low metabolic rate accompanied by very slight clinical symptoms aside from decrease in size of the thyroid. From this observation it would seem probable that many cases of hypothyroidism go undiscovered.

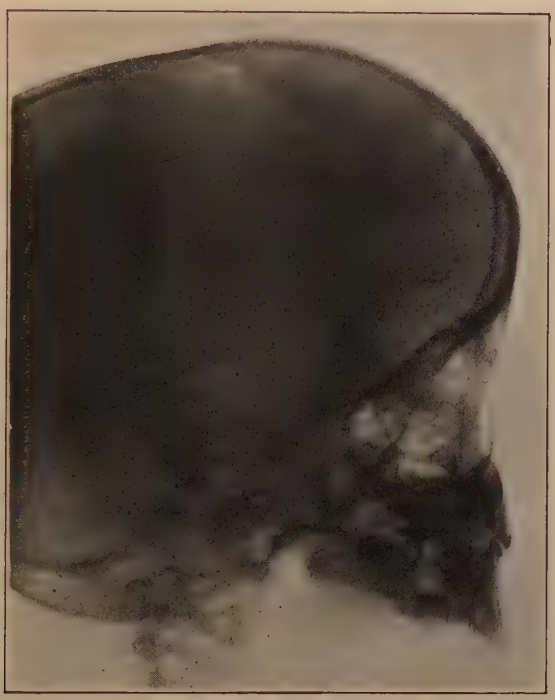


Fig. 18. Thin cranium and underdevelopment of facial bones in a cretinous boy of 5 years. Case No. 1939, see text. (N. W. Janney and H. E. Henderson. Archives of Internal Medicine, by permission.)

Familial Hypothyroidism.—The following three cases were children of one family. The family history was negative for thyroid disease except as noted. In seeking for the confirmation of the possibility of hypothyroidism in the children, the parents were examined and the father found to be a definite case of dysthyroidism, exhibiting small stature, defective hirsutes, frail nails, stubby extremities, exophthalmos, definite tremor, highly nervous disposition, but no goiter and a normal basal metabolism. The children came under observation merely on account of their failure to grow normally.

Case No. 1940, female, age 2 years; very poor sleeper, and an extremely nervous child. Birth and early growth were normal. By Sep-

tember 8, 1918, weight attained 24 lbs. 2½ oz. On January 20, 1919, weight was 29 lbs. 2½ oz., but had only gained 1 lb. 3½ oz. by September of this year. Physical examination is entirely negative but there was a general state of malnutrition which could not be accounted for by intestinal or other obvious causation. Special laboratory tests could not be carried out on account of the tender age. The child, in view of the affected family, was regarded as possibly hypothyroid, although a definite diagnosis could not be made. On minute doses of thyroid, general improvement was noted, the weight increasing one pound in 25 days' time, during October, 1919.

Fig. 19. Case 1939. Hands of cretinous boy of 5 years. Case No. 1939, see text. (N. W. Janney and H. E. Henderson, Archives of Internal Medicine, by permission.)

Case No. 1939, male, age 5 years, weight at birth normal; walked at second year, but not very well; began talking at 22nd month. Patient has always been subject to infections with slight provocation, having had bronchitis with colitis and slight attacks of asthma. Tonsils and adenoids had been removed on account of hypertrophy, but the former had partly grown in again. The patient occasionally exhibits patches of dry eczema. The mental development is much under that of his age. He is unreasonable, very nervous, flying into a rage for but little reason; showing, even for a child of his age, very defective memory. During the past two years, but three pounds of weight have been gained. He tires easily and appetite is

poor. Physical examination does not suggest typical cretinism, for the boy is over-thin, his face is narrow and pinched. The eyebrows are very scanty, the eyes and nose small, nares flaring, thyroid cannot be palpated, and the skin is dry. His abdomen is fuller than usual in contour; his gait is awkward, his body movements weak. His temperature is subnormal and pulse is 70. Diagnosis of hypothyroidism could be made in view of the family history and the signs present, with the help of röntgenological plates which exhibited marked underdevelopment of the bones of the skull

TABLE 1.—Nitrogen Balance in Hypothyroidism, Case No. 1938

Days	Weight in Kilos	Total Calories	Calories per Kilo	Food Nitrogen Grams	Urine N_2	Feces		Nitrogen Balance
						Grams	Total N_2	
1	25.7	1359.3	67.8	10.1	8.9	.....	.....	
2	25.0	1709.8	67.8	9.9	12.6	.....	.....	
3	25.0	1759.5	70.3	10.1	9.16	.....	.....	
4	25.2	1960.3	77.6	11.0	10.84	.....	.....	
5	25.4	1966.2	77.8	10.2	9.2	.....	.....	
6	25.4	1635	64.3	11.8	7.56	.....	.....	
7	25.4	1750	68.9	11.1	10.84	.....	.....	
Total	...	.....	...	74.2	69.11	95.8	4.48	plus 0.66 gm.
Daily average	...	.....	...	10.8	9.88	....	0.63	plus 0.093 gm.

TABLE 2.—Nitrogen Balance in Hypothyroidism, Case No. 1939

Days	Weight in Kilos	Total Calories	Calories per Kilo	Food Nitrogen Grams	Urine N_2	Feces		Nitrogen Balance
						Grams	Total N_2	
1	19.8	1451.2	75.9	8.04	9.7	.....	.....	
2	19.7	1503.8	75.9	7.8	11.6	.....	.....	
3	19.9	1523.5	77.3	9.6	12.58	.....	.....	
4	19.8	1957.3	88.1	9.9	6.25	.....	.....	
5	19.8	1959.3	91.3	10.1	6.25	.....	.....	
6	19.8	1550.7	78.0	10.1	10.5	.....	.....	
7	19.8	1526.5	77.0	8.1	6.48	.....	.....	
Total	...	.....	...	63.64	63.36	90.8	5.959	—5.95
Daily average	...	.....	...	9.09	9.05	....	0.835	—0.195

and face (see Fig. 18). Metabolic studies were carried out which demonstrated his inability to gain weight or nitrogen on a very full assimilable diet (see Table 2). There was great improvement on thyroid treatment.

Case No. 1938. Female, age 6 years. Growth was normal until 4th year, but only 3 pounds have been gained during the past 2 years. The child, superficially observed, has the appearance of perfect health. The face is normal in appearance; the nutrition is excellent; but on thorough examination there were observed thin, underdeveloped nails, tendency to decreased muscle tonus, a scarcely palpable thyroid, dry harsh skin, eczem-

atous patches on the skin, deficient perspiration and slightly protuberant abdomen. Metabolic studies were similar in result to those of her brother, except that the inability to retain nitrogen was not so marked. (See Table 1.) Röntgenologic studies showed bony structure and ossification centers normal for age. This case, in view of the family history, was regarded as probably hypothyroid, and was put through a therapeutic test. On treatment growth became normal, and from September 16, 1919, to December 28, 1919, the child gained 4 lbs. 14 oz., which is more than she had gained during the previous two years. This growth was attained on gr. ¼ daily of standardized thyroid extract.

This case is interesting on account of the slightness of the clinical signs and the prompt resumption of normal growth on a very small amount of thyroid substance.

Hypothyroidism in Adults.—*Masked Hypothyroidism in the Adult.*—Case 199, female, aged 36 years, married; no children. Of a neurotic family "of little endurance." Two cousins had pulses averaging 52 and 54. One, an under par individual, cured by thyroid treatment. Patient gives a history of normal growth, development and menstruation but has always been highly nervous and becomes exhausted on slight exertion. Occasionally is confined to bed for this cause. Though married 13 years, never became pregnant. Patient complains also of pain in base of neck and left shoulder. Is gaining weight slowly.

Physical examination: Facial expression neurotic, not myxedematous. Stature 5 ft. 9½ ins.; weight 188 pounds; but appearance not obese. Adipose tissue generally distributed. Flabby musculature. Cool extremities; skin and nails normal; hair distribution normal except hair on temples is very low and slight prolongation of *crines pubis* to umbilicus. Hands gracile, tapering fingers. Hips more adipose than rest of body. Thyroid somewhat small; normal to palpation. Somatic organs normal. Chronic inflammation of tonsils only demonstrable seat of possible focal infection. Blood pressure normal. Temperature 96.6. Pulse 56; respiration 16. Laboratory Data: Urine and blood count negative. Differential count: polymorphonuclears 62, lymphocytes 34, large mononuclears 1 1/3, eosinophiles 2/3, basophiles and transitionals 2, per cent. On a Schmidt test diet of three days' duration, the stools were essentially negative. The basal metabolism ranged from —10 to —20 by small Benedict apparatus, six observations. Röntgenological examination, a normal sella turcica measuring—width 13 mm., depth 10 mm. The cervical spine showed an abnormal prolongation of the transverse process of the 7th cervical vertebrae, that on the left side being ¼ inch longer than the right transverse process. Long bones negative. Epiphyses normal closure.

Clinical Résumé: Neurasthenia is strongly suggested by the family and parents' histories. An apparent or exciting cause is not lacking for

the discovery of a cervical rib makes a secondary general neurosis not unlikely. The pain in the neck and shoulder is accounted for by the presence of the rudimentary cervical rib. The possibility of a chronic colitis with intestinal toxemia was eliminated by the negative results of the Schmidt dietary régime. The height, gracile hands, fat and hair distribution suggest the possibility of dyspituitarism or ovarian dystrophy, which might also account for the decreased basal metabolism, the leucocyte formula and sterility. The family history of slow pulse and beneficial results of thyroid treatment in the case of a cousin is suggestive of familial hypothyroidism. Only the slowness of pulse, temperature and respiration, the asthenia and sterility are indicative of hypothyroidism. The lowered basal metabolism and abnormal leucocytic formula rendered the diagnosis possible. This diagnosis was confirmed by the therapeutic test. After one month's treatment of 0.4 mgm. thyroxin (Kendall) daily, complete recovery ensued except for the pains in neck and shoulder due to the cervical rib. The basal metabolism was maintained at the normal level. Patient's temperature, pulse and respirations rose to normal. Evidently the neurasthenia in this case was an expression of hypothyroidism. On account of the good result of thyroid therapy, additional clinical and therapeutic studies of the possible presence of other endocrin dystrophies were not undertaken.

An interesting feature in this case was that conception took place during the first year of thyroid treatment. About the fourth month of this normal pregnancy, the neurasthenia and asthenia returned, although the obstetrical condition was satisfactory. The patient was regularly taking 0.4 mgm. thyroxin daily. Basal metabolism rate fell again to —20 but rapidly rose to normal on increasing the dose of the thyroid hormone to 0.8 mgm. which was followed by a subsidence of the hypothyroid symptoms. The amount of thyroxin available on the lower dosage evidently did not suffice for the added requirements caused by the developing fetus.

Cachexia Strumipriva.—Case 1960, female, nurse, aged 40 years, single. Family history: Mother asthenic, obese, glycosuria at times; a niece was a goiter. Patient's history: A highly strung, sensitive child. Graves' Disease developed at 17, which persisted until the 31st year when right lobe of thyroid and isthmus were removed. The thyrotoxic symptoms gradually subsided during the first post-operative year, the pulse falling to 70 from 140 pre-operative.

Hypothyroidism then gradually developed; asthenia, mental hebetude, inability to carry out duties, uncontrollable gain of weight to 140 pounds. At 33rd year, diagnosed hypothyroid. Symptoms relieved by gr. 2 thyroid extract daily, weight falling to 123 pounds. Has taken thyroid extract irregularly since. Much larger doses fail to relieve patient at present.

Physical examination: Typical, well developed myxedema. The eyes

show exophthalmos and Stelwagen's sign, probably as a result of former Graves' disease; moderate obesity, very flabby musculature. No portion of thyroid gland is palpable in neck beneath lobectomy scar. Heart, lungs, abdomen negative. Blood pressure 135/85; extremities and skin cold and cyanotic. Pulse 76; temperature and respiration normal.

Laboratory Data: Urine and blood count normal. Hemoglobin 70 per cent (Sahli). Differential blood count, lymphocytes 38 per cent, large mononuclears 3½ per cent, polymorphonuclear leucocytes 55 per cent, eosinophiles 1⅓ per cent, basophiles ⅔ per cent, transitionals

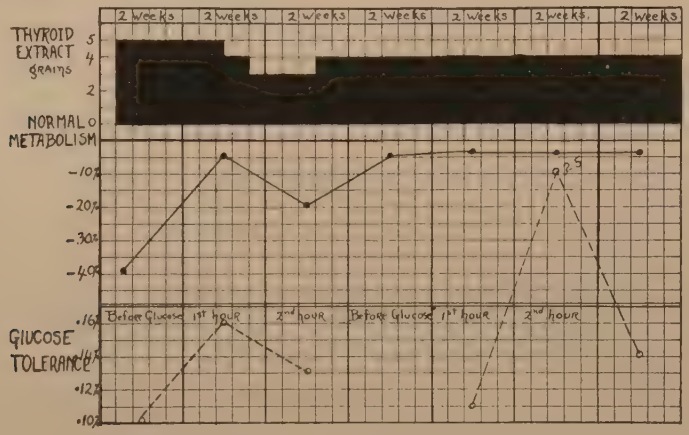


Fig. 20. Masked Hypothyroidism. Inability to gain nitrogen and weight on abundant diet. (From Janney and Henderson, Arch. Int. Med., Vol. xxvi, pp. 297-318, 1920, by permission).

1⅔ per cent. Initial basal metabolism —38 by small Benedict apparatus. The blood sugar curve was decidedly abnormal.

The case is of interest on account of the family history which suggests a congenital defective thyroid function which may have predisposed to the grave myxedema following lobectomy for Graves' disease.

The course of the case under thyroid treatment with *regular* control by the basal metabolism is an excellent example of the great aid of this physical method in control of the treatment (see accompanying chart and legend). As the general result of treatment, the dosage of thyroid extract could be accurately determined; the basal metabolism was permanently reëstablished at the normal rate, the patient's health became practically normal and she was able to carry out her duties in a highly satisfactory manner. She still showed certain of the signs of hypothyroidism, pallor, transverse seaming of forehead, deficient eyebrows, coarse skin, etc. This is rather to be expected in a case of seven years' duration with previous intermittent and unsatisfactory treatment.

The Cretinic Degeneration

NELSON W. JANNEY

LOS ANGELES

Definition
Historical
Geographical and Orographical Distribution
Prevalence, Economic and Military Importance
Endemiological
Epidemiological
Etiology
Pathology
Symptomatology
Diagnosis
Treatment

Definition

The Cretinic Degeneration may be defined as an endemic disease characterized by goiter, cretinism, deaf-mutism, idiocy and caused by toxins probably of bacterial origin usually introduced by impure water or contaminated soil. Certain epidemiological, etiological, pathological and clinical features of this disease are at such variance as to preclude an absolute identity with hypothyroidism which, however, plays a dominating rôle in many cases. The relation to hypothyroidism will be developed in the section on etiology.

Historical

Goiter was known to the Romans, as various mention of this striking condition is made in the works of Pliny, Juvenal, Vitruvious, Ulpian, who commented upon its endemic occurrence in the Alps. "Quis tumidum gutter miratur in Alpibus" (Pliny 13th Satire). It was regarded as a punishment of the gods. Through the dark ages little mention of the disease is made in the literature. In the 13th century Marco Polo, the celebrated traveler, called attention to the frequency of goiter on the plateaus of Central Asia. Several descriptions of the disease appeared in

the 14th and 15th centuries of which that of Paracelsus was epoch making. This writer described goiter and endemic cretinism in the Salzburg region where it still remains endemic, and emphasized as well the intimate relationship between these expressions of endemic cretinism. In the literature of the 16th and 17th centuries a number of superficial observations appeared on the occurrence of the disease in various endemic areas in Europe. Careful studies of the disease were furnished by a coterie of authors at the end of the 18th and beginning of the 19th centuries, among them Saussure, Malacarne of Turin, Foderé, Ackermann and the Wenzels. Keeping pace with the rapid development of medical knowledge during the 19th century, there has been contributed during this time a voluminous literature on the endemiology, etiology and pathology of Cretinic Degeneration, the mere enumeration of which would exceed the size of the present article. The contributions of the following are of especial significance: Bircher, Coindet, F. Meckel, Huscke, Maffei, His, Dohrn, Eulenberg, Lebert, Koelliker, Klebs, Kocher, Lücke, W. Mueller, Oswald, St. Lager, Woelffler.

The geographical and endemiological data of endemic cretinism have been classically presented by A. Hirsch, whose monograph should be consulted. Of late monographs and articles, those of Ewald, V. Wagner, Lobenhoffer, Dieterle, Scholz, Wagner v. Jauregg, Siegert, Thomas, Wieland, Crotti, McCarrison, Dock, Falta, Marine and Lenhart, also Gaylord, are of especial importance. (See Bibliography.)

Geographical and Orographical Distribution

The geographical distribution of endemic cretinism has of itself been the subject of a large literature among which the monographs of Hirsch, Bircher (*a*) and McCarrison (*d*) (the two latter with maps) are of especial value. The chief foci of endemic cretinism in Europe are the Central Alps from which endemic areas radiate in various directions. Thus the disease is common in Switzerland, the Tyrol, Carinthia, Steiermark, the Savoy, Basses-Alpes, Alpes-Maritimes, Haute Garonne. There are also a number of secondary centers situated in mountainous districts or deep valleys, such as the Carpathians, the Vosges, Cevennes, the German mountains, the Pyrenees, the English Pennine, Cotswold and Mendip ranges, though the disease is rare in the Scottish Highlands and the Norwegian mountains. The tendency of the disease to appear in mountainous districts is not limited to Europe for marked endemic areas are found in the Caucasus, the Ural and Altai ranges, the Himalayas, the Abyssinian mountains, the Andes, Cordilleras, the mountains of Japan and the Asiatic islands.

The cretinic degeneration is, however, by no means confined to the

mountainous areas, for the disease flourishes in the plains of Lombardy, Piedmont, Venice, Alsace. River and lake basins and deltas may likewise be favored. Such are those of the Struma River in the Balkans, so named from the prevalence of goiter on its banks (Crotti), the Lena and Obi in Russia, the Ganges, Indus, Brahmaputra and other Indian rivers, the Great Lakes and the St. Lawrence in America. Crotti mentions a river in Brazil called the *Guay-qui-raro* or "Thick neck maker" on account of its goitrigenous qualities.

Several writers call attention to the prevalence of the disease in marshy regions and inundated areas, along canals. If one bank of a river is a marshy region, the other high land, the former will be affected (for example, the Ganges). Islands may have endemic foci, even those such as the Azores at great distance from other land. In Madagascar, Ceylon, Borneo, Sumatra, Java, the disease is known.

The sea coasts, though formerly claimed to be entirely free from goiter and cretinism are occasionally affected. McCarrison quotes the following endemic littoral regions, the Ganges delta, the Island of Cutch in Manila Bay, the Island of Arran off the coast of Algeria, Glamorganshire, certain shores of the Mediterranean, such as Istria and Dalmatia.

Altitude bears no direct relationship to the presence of cretinic degeneration as it is found all the way from the sea level to the Himalayan villages situated over 10,000 feet above sea level (McCarrison), or even up to 15,000 feet in Nepal and Kashmir (Crotti). Foci of the disease are frequently found half way up the sides of steep valleys and less often on high tablelands. The association of endemic goiter and cretinism with certain geologic strata has been the subject matter of so much speculation that this subject, with other theories as to causation, is best treated under the section "Etiology."

Prevalence, Economic and Military Importance

From point of numbers of inhabitants affected, cretinic degeneration is one of the most common of all morbid conditions. In certain endemic regions of Switzerland, Austria and India, it is to be regarded as the most frequent of all diseases, for practically every inhabitant is more or less affected.

Its economic and military significance has become of great moment and has led to the appointment, in England, France, Switzerland and Italy, of commissions for the special study and research of its etiology and prevention. So much data has been collected upon the matter of prevalence that it has become unwieldy for detailed presentation. A few notations may here suffice.

In Switzerland about 3,000 recruits are annually rejected for causes

attributable conservatively to endemic cretinism which during ten years would amount to nearly one-fourth of the Swiss army (Oswald). In 1883 among a total population of 9,565,038 in the Italian provinces Piedmont, Lombardy and Venetia, there were 12,882 cretins and 128,730 goitrous (Ewald). In severely affected districts, such as Murau in Steiermark, Austria, 1 per cent of inhabitants are cretins (Ewald). In France, according to Baillarger's statistics (1873), 370,403 goitrous and 120,700 cretinous inhabitants existed in a population of about thirty-six millions. McCarrison states, "In some Himalayan villages the disease is so common that it is difficult to find a man, woman or child not suffering from the deformity (i. e., goiter). In India at the present time not less than five million persons are afflicted with goiter, while half a million is a low estimate of the numbers who suffer from its congenital manifestations." The disease is common in England in Hampshire, also in Sussex, and so frequently met with in Derbyshire as to give to goiter the nickname of "Derbyshire neck."

For the United States, little statistical information is available which is due to the mildness of the cretinic degeneration in this country. Substantiated cases of endemic cretinism the writer has not found reported in the literature, while the endemic goiters are usually small, often escaping popular observation. Dock has reported an incidence of two to three goiter per 1,000 and 10 per cent among young women. This embodies simple goiter of various causation. Munson reported up to 2.36 per cent in the American Indian population. Adami, Marine (*a*), Osler (*a*) report the frequency of goiter in the Great Lakes region. Adami mentions its great prevalence in certain French Canadian villages. In West Virginia it is frequent, Clark and Pierce in 1913 finding 1,234 cases of goiter among 13,836 school children. In Virginia 12.7 per cent (817) cases were found among 6,432 goitrous public school children, the incidence in Carroll County, Va., being 23 per cent. No cases of cretinism were found in either state. Negroes were also affected severely. In the colored high school at Charleston, W. Va., every girl of the senior class suffered from goiter. Less than one-tenth of one per cent of goiter in this report of the disease in the Virginias was found to occur in boys. In certain of the Western states, particularly Nevada, California, Oregon and Washington, small goiters are quite common according to the U. S. Army statistics of W. J. Kerr among 21,000 troops. Twenty-one per cent showed definite thyroid enlargement, but among them were included cases showing thyrotoxic symptoms.

The world's incidence of cretinic degeneration is in all probability generally decreasing in indirect ratio with the improvement of water supply and hygiene. This fact is difficult to establish statistically.

In severely affected localities and countries, the presence of large numbers of helpless endemic cretins, idiots and deaf-mutes entails the

burden of supporting large state communal and private institutions for their care. Many of the less afflicted are withheld through their mental or physical deficiencies from productive vocations. Again, many large commercial companies refuse to employ those rejected by military examiners with the result that such young men are often forced into vocations beneath their actual ability, thus again entailing economic loss. The sociologic and economic burden imposed upon a community or state by such a prevalent disease is enormous. The loss to the military of numerous recruits due to this disease is of grave significance in countries where the disease is common and severe.

Endemiological

Endemicity is a characteristic feature of the disease. There is great variation in the intensity with which the inhabitants of various countries, districts, and even villages, are affected. Certain countries, such as the United States, may have large areas free from endemic goiter and cretinism. On the other hand, the disease may elsewhere exhibit such great intensity that practically none of the inhabitants of an endemic area may entirely escape. Endemic goiter may be regarded as the lightest clinical expression of the disease. In many affected regions, cretinism, deaf-mutism and goiter heart may be quite absent. Where the disease presents its maximal intensity nearly all the inhabitants are goitrous and the severer clinical forms are found always, however, in much less numbers than merely goitrous individuals. Adjacent villages in endemic areas may present great differences in this regard. In one, only goiters may be encountered; in another but a short distance away, cretins also may be found.

A very slow ebb and flow of the endemic may be observable. Usually the lack of precise data renders it difficult to follow such fluctuations in severity, which develop over a long period of years. In this regard, Baillarger's extensive statistics are of great value. This writer found that during a period of 50 years ending 1865 that in the 60 departments of France, the incidence of endemic goiter increased in 26 departments, decreased in 17 and remained *in statu quo* throughout the remainder. It seems as if a period of maximum intensity leads to a certain degree of auto-immunization which tends to check further development and brings about a gradual recession. Indeed, an endemic area may become practically free of the disease, with only a few cases of goiter persisting. This may be induced by hygienic measures, particularly the introduction of a pure drinking water supply.

Endemics of cretinic degeneration are much more frequent in rural

districts. Its severer clinical forms are rarely met with in large cities though its lighter expressions are common in Vienna, Innsbruck, Berne and Beyreuth, also certain cities of India.

New regions may become affected within a reasonably short time. McCarrison (*a*) describes an interesting epidemic in Nagar, India, introduced through the arrival of a goitrous family. By slow development in seven or eight years thereafter 31 individuals of a total population of 1,500 had acquired the disease. The source of infection was traced to a spring of drinking water. In Brazil goiter did not exist previously to 1830 in certain districts (Natividad, Rio Grande do Sul) in which the disease is now endemic (Crotti). There are many other localities where changes in the endemic can be verified. A decrease in endemic goiter has been observed in certain parts of Switzerland, the Rhinelands, the Harz, Franconia, Thuringia in Germany; in the Pyrenees in Spain; in Ferrara, Bara and parts of northern Italy; also in some sections of Sicily. Goiter and cretinism have disappeared from the Rhenish Island of Niederwörth where formerly nearly all inhabitants were affected. In the valley regions near Granada, Spain, goiter began to appear in the early part of the last century and has greatly increased (Crotti). Ewald, Roesch, Kutschera, *et al.* cite other examples of fluctuations of the endemic.

Newcomers into an infected area are usually more susceptible than the older inhabitants. Removal from an affected area usually leads to diminution or disappearance of the symptoms. Frequently healthy children will again be born to goitrous parents, even to those who bore cretins while living in an endemic region. During the early period of the endemic, variations are apt to occur in the size of the goiters.

Epidemiological

It is questionable whether "goiter epidemics" ever occur except in endemic areas. Probably such exacerbations of the disease are best regarded as rapid endemiological fluctuations due to unusual conditions such as the sudden introduction of large numbers of new and susceptible individuals in a badly affected community, particularly when the added etiological factor of unhygienic surroundings is present in addition. These outbreaks often take place in institutions such as boarding schools, prisons and military barracks, where crowding, intimate personal contact, unsanitary water supply and sewage disposal becomes etiologically important.

Crotti recounts a particularly interesting epidemic development of goiter among the sailors during Captain Cook's voyage of exploration in 1772, reported by the ship's surgeon, Forster. While their vessel lay among icebergs, the crew used bits of ice therefrom for drinking purposes. Such of the sailors who partook of the ice developed goiter, the remainder

escaping. It is likely that the ice was derived from a goitrous fresh water source.

Of military epidemics there have been many reported in the older literature. It is a striking fact that in spite of the millions of men engaged in the recent World War, such outbreaks scarcely seem to have occurred. This contrast is probably ascribable to the infinitely improved hygienic surroundings and food supply of soldiers in the twentieth than in the eighteenth or even nineteenth century.

Of the many military outbreaks of goiter, an account of one of the most interesting must here suffice. The development of goiter in an infantry regiment sent to Nancy in 1783 was reported by Valentin and cited by Lebert and others. Goiter is mildly endemic in this locality. During the winter of 1783, 38 men developed goiters. The number affected gradually increased until, in 1786, 425 had acquired the disease. In 1787 the epidemic diminished, the number of cases falling to 257 and in 1788 to 132 cases. It terminated in 1789 with 43 cases. The private soldiers alone were affected, the officers being exempt though quartered in the same barracks. The immunity of the officers to the disease has been ascribed to the greater opportunity for wine drinking, therefore less water intake on the part of the officers; but also, according to Taussig and Kutschera, to the more isolated quarters and consequent less close and frequent contact with goitrous individuals.

The observation of Cardinal Billiet in the normal school of Albertville is quoted by H. Bircher. In a girls' school to which use the building was put for twenty years previous to 1860, goiter was unknown. During this year improvements were made and a normal school instituted, the building débris being thrown carelessly near the well. From twenty-five to thirty per cent of the pupils became goitrous within a short period. When rain-water instead of the well-water was used for drinking purposes, the goiters promptly disappeared.

Etiology

Influence of Heredity.—Congenital goiter is the most frequent hereditary manifestation of the cretinic degeneration though it is much less frequent than the acquired, the ratio being about 1:17 for Switzerland (Demme). The frequency varies in various districts, however, and directly with the gravity of the disease. In severely affected Himalayan villages as high as sixty per cent of breast-fed children show congenital goiters. On the other hand, cretinism in the offspring is usually preceded by goiter in the parent. Ninety-six per cent of the mothers and forty per cent of the fathers of cretins had goiter (McCarrison). This writer also ascribes mental shock, worry and depression, also disease of the mother as etiologically important. With regard to the etiologic rôle played by disease,

it is well to remember that the lowered resistance of the goitrous individual invites ready attack by bacterial and other toxic agents, so that chronic infections and intoxications are probably to be best regarded in many cases as accompanying phenomena as well as causative factors in the production of cretinic degeneration in the offspring. Be this as it may, statistics have definitely established an etiologic relationship between goiter in the parents and cretinism in the offspring. Later researches have demonstrated the low iodin content of goiters, therefore their low hormone content and probable sub-functional condition of such thyroid glands. It would seem therefore that the development of congenital goiter may be compensatory as well as possibly due to hereditary lack of normality in the thyroid apparatus of the child. These factors are apparent from Horseley's experiments in which goitrous puppies were born to partially thyroidectomized bitches.

Age.—Endemic goiter may develop at any age, though its incidence is least during the first years of life. Its incidence gradually increases to the fourth decennium, then decreases. In spite of statements to the contrary of Kocher and other Swiss writers, it has been demonstrated statistically that endemic goiter is much more frequent among adults than children in about the proportion of 2:1 (Bircher, Baillarger). It is less common before puberty. Most authors agree that endemic cretinism requires a certain length of exposure in an endemic community for its development as Wieland carefully emphasizes. It thus differs from sporadic athyreosis and congenital hypothyroidism which can often be detected in the first months of the life (E. Wieland). The age of predilection in the later years of childhood is from the 7th to the 10th year. The incidentality then slightly diminishes to rise again at puberty. Children are apparently more frequently affected in beginning epidemics than adults. In a goiter epidemic in a village of 1,500 inhabitants, of the 31 cases affected, 29 were under sixteen years of age (McCarrison). Endemic goiter and cretinism are rare among old people who have not developed the disease previously.

Sex.—During childhood the incidence of endemic goiter is about equal among boys and girls. From puberty onward, the female sex is most often affected, the ratio being stated from 2:1 to 6 or 8:1 by various statisticians. Puberty and gestation predispose to goiter. During pregnancy goiters may greatly enlarge, declining again in size thereafter. Pregnancy in normal women is, however, known to cause thyroid hypertrophy in a number of cases. Even menstruation may cause thyroid swelling. The sex incidence is much influenced by the severity of the endemic. In lightly affected communities women are more susceptible. When the disease is very severe, both sexes may be equally attacked.

Race.—All races, Caucasian, Mongolian, Malayan and Negro, may be affected. The apparent greater incidence at times noted among

members of a given race in a given country will be found to be due to other causes.

Occupation.—Manual laborers, particularly those exposed directly to soil and water contamination, are particularly prone to the disease. Mackenzie found 98 per cent of the endemic goiters of Lanarkshire among the laborers and miners. In a rural community the clerks and other indoor workers escape to a greater degree than do the agricultural classes even when no difference of hygiene and general environment exists.

Acute and Chronic Diseases.—Among such may be mentioned acute and chronic infections and intoxications, some of which may have been demonstrated to cause petechial and sclerotic lesions in the thyroid gland. It is, however, difficult to estimate accurately the amount of damage done by such agents. The specific action of infectious diseases would be to injure and diminish the amount of functionating thyroid parenchyma, thus predisposing to the hypertrophic influence of the specific causes of cretinic degeneration. As the gastro-intestinal tract has been demonstrated by McCarrison to be a portal of entry of the toxic agents producing goiter and cretinism (see below) more exact future observations may demonstrate the rôle of chronic inflammations of the digestive canal such as catarrhal colitis, as predisposing etiologic factors.

The *Influence of the Seasons* bears a relation to the variation in the iodin content of the thyroid, lowest, according to Seidell and Fenger's (*b*) researches, during the first four months of the year. It is then that goiters reach their maximal size by a process of compensatory hypertrophy. Outbreaks of "Spring" or "Summer" goiter are not uncommon among newcomers in European endemic centers. They may be possibly due to contamination of the water supply by the spring rains or to a low spring and summer iodin content of the affected thyroids. In animals seasonal variation in goiters has been traced to the low iodin content of food at certain seasons. In countries of dry and rainy seasons the disease is more prevalent during the wet period owing to contamination of the water supply by surface water.

Other Predisposing Conditions.—The thyroid gland is probably the most important regulator of metabolic processes. Any factor which influences deleteriously the general metabolism or its nervous control will of itself bring on added strain on this endocrin organ. Such are insufficient food, air, space, residence in high altitudes (insufficient oxygenation), great nervous and emotional strain, oversexual activity, gestation, etc.

The Relation of the Thyroid Gland to the Cretinic Degeneration.—Two theories as to the relation of the thyroid gland to the cretinic degeneration have been evolved. One viewpoint would recognize cretinic degeneration merely as an endemic expression of hypothyroidism (Kocher, v. Wagner, Combe, v. Jauregg, v. Eiselsberg, Hertoghe, Bayon, McCar-

rison, de Quervain, Knöpfelmacher, Siegert, *et al.*). These authors champion the so-called *unitarian conception.* Opposed to this theory is the so-called *dualistic conception,* according to which endemic cretinism and its accompanying conditions are regarded as a general process of degenerative nature affecting various tissues and organs including the thyroid. Among the "Dualists" may be mentioned H. and E. Bircher, Pineles, Scholz, Wieland, Dieterle, v. Kutschera, Falta, Crotti, etc.

The unitarian hypothesis was strongly supported by Kocher as early as 1892. It emphasizes the frequency of goiter and cretinism in the endemic disease and regards deaf-mutism, idiocy, goitrous degeneration of the thyroid and infrequency of myxedema merely as deviations from the typical picture of hypothyroidism due to the influence of heredity and endemicity. The excellent results obtained in extensive series of cases treated by thyroid extract lends further support to this theory. In spite, however, of these data and of much ingenious explanation by the supporters of this theory, it seems difficult to include under hypothyroidism all clinical forms of cretinic degeneration. For example, the nervous type of endemic cretinism of India described by McCarrison presents spastic diplegia which is not met with in hypothyroidism.

The earlier supporters of the dualistic view maintained that the cretinic degeneration differed fundamentally from sporadic hypothyroidism and even went so far as to deny any relationship between these two conditions. Of late, however, there has been a tendency to give proper importance to the prominent rôle played by the thyroid in endemic cretinism and allied disorders. The dualists emphasize, however, a number of differences, which render it impossible to regard the cretinic degeneration simply as an endemic expression of hypothyroidism. These points of divergence as contrasted to sporadic cretinism are as follows:

1. The usually later onset of endemic cretinism speaks for a different causation of exogenous nature.

2. Variability and indefiniteness in the clinical symptoms as contrasted to the exceptional regularity and definite nature of the manifestations of hypothyroidism.

3. Failure of parallelism between the severity of the clinical symptoms and the thyroid pathology.

4. Less delay and marked irregularity in the ossification processes of cretinic degeneration as compared to the skeleton in sporadic hypothyroidism.

5. Special clinical characteristics. Such are the frequency of deaf-mutism, idiocy, goiter-heart, and large degenerated goiters.

6. Absence in endemic areas of cretins with *typical* sporadic signs and symptoms. Absence or slight expression of myxedematous symptoms in many cases.

7. Frequent involvement of other ductless glands, particularly the hypophysis and parathyroids.

8. Failure to regularly obtain the excellent results which follow thyroid therapy in sporadic hypothyroidism.

The most plausible explanation advanced to account for these differences between endemic cretinism remains then in substance to-day the same as first expressed by Ewald as early as 1896, who regarded the cretinic degeneration as a chronic degeneration affecting the organs in general, also the thyroid gland. This view is held by most authorities at present and has received additional support by recent experimental researches.

Theories as to the Etiology of the Cretinic Degeneration

The development of hypotheses and theories in regard to the pathogenesis of cretinic degeneration has paralleled the expansion of medical knowledge in general. The older views attributed endemic goiter and cretinism to a multitude of fantastic factors none of which can resist the light of modern scientific investigation, although many are fraught with great medical, historic and literary interest. It is surprising that so much space has been given these hypotheses, even in modern text-books.

The theories as to the pathogenesis of cretinic degeneration have been ably presented by a number of writers on the subject. Among them, Crotti in his recent work on "The Thyroid and Thymus" has critically analyzed the various standpoints in a masterly fashion. In a work of the present dimensions, it is only possible to give a brief summary of the most pertinent material.

The Relation Between Water Supply and the Cretinic Degeneration.—No single fact concerning the etiology of this disease is more firmly established than the water-borne nature of the causative agent. The production of goiter and cretinism by drinking from "goiter-wells," "goiter-springs" and brooks has been known from antiquity. Newcomers into a community using such water become goitrous, conversely the removal from such a community is followed by diminution of goiter and cretinism. The introduction of a pure water supply acts in a curative manner. Of the many interesting examples quoted in the literature, two must suffice. The account of E. Bircher (*a*) of the improvement taking place in Rupperswil, a village of the Aargau, after the introduction in 1883 of a new water system from a goiter-free locality has become classic.

In	the	year	1885	there	were	59	per	cent	of	goitrous	school children
"	"	"	1886	"	"	44	"	"	"	"	" "
"	"	"	1889	"	"	25	"	"	"	"	" "
"	"	"	1895	"	"	10	"	"	"	"	" "
"	"	"	1907	"	"	2.5	"	"	"	"	" "

There were many cretins and deaf-mutes previous to 1885 who gradually disappeared in the years succeeding the introduction of the pure water supply.

As another striking instance of the influence of the water supply can be quoted John W. McClelland's report of an endemic in Deoba, India. The Brahmins or highest caste of the population obtained their drinking water from a distant spring of high purity. They were entirely free from the prevailing goiter endemic. The middle class (Rajputs) drank partly good and partly goitrigenous water. Two-thirds of this class were goitrous. The lowest class (Domes), who depended for their entire water supply upon the local goitrigenous springs, all acquired thyroid hypertrophy.

The noxus collects in the sediment of reservoirs while the supernatant water may be innocuous. An interesting example of this action is given by Thea for the town of Cuneo in Italy. The population was goiter-free. It secured its water supply from the upper part of the last basin of a system of reservoirs. Of the garrison, 40 per cent became goitrous during a period of 8 years. It was found that the soldiers were drinking unsedimented water. On obtaining their supply in the identical fashion from the general town system, the goiter epidemic disappeared.

The Chemical Hypotheses.—The intimate relationship between the development of endemic cretinism and the water supply has become the common basis for several widely divergent etiologic theories. Thus the disease was at first attributed to chemical constituents of the water. Grange considered magnesium, St. Lager iron and copper pyrites, McClelland and others, calcium salts as the special causative factors. Even iodin, now known to be a curative agent, dissolved air, carbon dioxid, etc., have been considered in this regard. Further investigation has, however, always disproved these hypotheses. The goitrigenous quality of water does not in general depend upon the mineral content. Hard waters may lead to increase in size of goiters, but this is only to be regarded in the light of a predisposing etiologic factor.

The Hydrotelluric Theory, though already advanced by many, received its greatest support from H. Bircher in his important monograph on "Endemic Goiter" published in 1883. Bircher concludes that:

1. Goiter occurs only upon marine deposits and those especially upon marine sediments of the Paleozoic, Triassic and Tertiary periods. The remains of the extinct flora and fauna of these geologic ages are regarded as the ultimate cause of the disease.

2. That the eruptive rocks, the crystalline rocks of the Archean period, the sediments of the Jurassic, Cretaceous, and Quarternary seas and all fresh water deposits are free from goiter. The mountainous endemicity is explained by the protrusion in such districts of rocks of the first description.

Though it is generally true that cretinic degeneration occurs with predilection on such limestone formations as indicated, yet very many unaffected communities and regions are underlain by the same rock strata. Moreover, it is now known through the researches of Hesse, Schittenhelm and Weichardt that Archean and eruptive strata are by no means free of goiter, which definitely disproves the hydrotelluric theory as no organic material whatsoever can be washed out of such rocks.

The consensus of present authority discredits the geological hypothesis of Bircher, though he and others brought together much evidence in its support. There remains, however, an explanation to be sought for the frequency of occurrence of the cretinic degeneration upon the Paleozoic and other limestone strata. McCarrison (*a*) tersely summarizes the modern viewpoint of this question when he states:

"The explanation of the frequent association of goiter with limestone rocks is that they are amongst the most porous, as well as the most widely distributed, of all geological formations. They are thus amongst the most freely cultivated and inhabited, and their porosity favors the passage of the excitants of the disease to unprotected water-supplies. Waters derived from such rocks may contain an excessive quantity of lime, the ingestion of which, while not actually the cause of goiter, throws an additional burden on the functional resources of the thyroid gland. The presence in the soil of decaying vegetable or animal matter may convert any soil, no matter what its geological origin, into a suitable habitat for the *contagium vivum* of the disease. A manure heap or a cess-pit, for example, will be far more effective in this direction than the remains of extinct flora or fauna."

The Plutonian Theory of Repin is closely associated with the foregoing. Répin assumes the important characteristics of mineral waters to be their general effect upon metabolism, their emergence from deep fractures of the earth's crust, their increased radioactivity and their lime content. This author believes goitrigenous waters to be always such natural or eruptive waters and weaves a complex hypothesis based upon these views.

This ingenious speculation is disproven by many facts now well known, for example, the fact that soft water, even rain water, may produce goiter under some circumstances (McCarrison). This fact also strongly militates against Bircher's hydrotelluric theory. It may be added that Hesse has disproven any etiologic connection between radioactive waters and the cretinic degeneration.

The Organic Theory of Goiter.—Of recent years, attention has been more and more directed toward the possibility of an *organic* etiology.

Lustig and Carle, the Swiss Goiter Commission, E. Bircher (*c*),

McCarrison (*d*), have produced goiter experimentally in animals and man through drinking goitrigenous water or from the residue of such water on a Berkefeld filter. After such filtration, goiter still can be produced, so Wilms, who developed the so-called "organic theory of goiter" concludes the toxic agent must be a toxin or toxalbumin or organic ferment from organic substance, especially as boiling or heating over 70° destroys its toxicity (E. Bircher, Wilms, Breitner, Lobenhoffer, McCarrison). Dialysis removes the goitrigenous agent from water, the substance collects upon the membrane of the dialyser and centrifugalization renders the water innocuous.

The Theory of Direct Contagion has been advocated by A. Kutschera, L. Taussig among others. Kutschera (*b*) bases his views upon the strong familial, house, or locality tendency of the disease, stating that it is only present where there has been opportunity for direct personal contact. This author denies that the disease is so closely bound to the water supply of certain communities as has become firmly fixed in the minds of laymen and physicians but rather depends upon transmission through bedding, clothing, etc. He cites instances, as does McCarrison, of a spread of the disease from the introduction of a goitrous individual or cretin into an unaffected community. As an important example of the house mode of infection is quoted the description of Fradeneck in 1844 of the endemic cretinism in the Tostenhuben community dwellings of Sirnitz, Carinthia. At the time of this description, practically all who lived in these dwellings were cretinous. Later the buildings were partly rebuilt after a fire in 1847 and partly refinished. After these occurrences, goiter and cretinism disappeared. The water supply remained the same throughout. Kutschera correctly concludes from this and many other examples that the disease is communicated by personal contact. He cites the parasitic thyroiditis described by Chagas in Brazil which is caused by a trypanosome, *schizotrypanum cruzi,* and transmitted by a biting insect. The chronic forms of this disease are characterized by goiter although some doubt of the accuracy of Chagas' observations in this regard is expressed by McCarrison. Taussig (who supports the contagion by contact theory) compares the endemicity of the cretinic degeneration in Bosnia to that of leprosy and syphilis which have been proven contact diseases in the same country where his studies were carried out. In this Austrian province all three diseases are especially prevalent among the rural Mohammedan population who cling to a primitive manner of life, families sleeping huddled on the floor of the same room, eating and drinking from the same pot without separate utensils. To the truth of these statements the writer of this article can also testify. On a visit to the interior of Bosnia, he was astonished at the filthy mode of life. Taussig quotes many examples of garrisons and other hygienic dwellings in this country where in spite of the same water supply and much goiter being generally present the

soldiers and inhabitants who dwelt in this better environment escaped the disease.

Kutschera, Taussig and others have made important contributions in emphasizing the probability of a direct contagion as the etiologic agent of cretinic degeneration but tend to obscure the issue somewhat by undervaluing the importance of water as a common mode of infection.

The Bacterial Theory.—A further and perhaps final step in the development of our knowledge of the etiology of cretinic degeneration has been made by Major R. McCarrison (*d*) of the Indian Medical Service whose studies of the disease have extended over a decennium in India as well as including visits to the European endemic areas. His writings have been collected in the Milroy Lectures in the *Lancet,* 1913, and his monographs, "The Etiology of Endemic Goiter," 1913, and "The Thyroid Gland," 1917. Perhaps it is due to the remote country in which McCarrison's important researches were carried out that they have not been as largely disseminated in the literature and in the scientific medical world as they would otherwise have been. McCarrison believes that cretinic degeneration is usually due to fecal bacteria or their toxins emanating from the alimentary canal of man. Though fully appreciating that water is the chief mode of infection, he likewise ascribes due importance to direct contact, house and soil infection. McCarrison bases his theory upon his personal observations on endemicity in India, his experimental production of goiter in man and animals by goitrigenous water, and by water contaminated by feces of goitrous and cretinous individuals; also upon similar animal and fish experiments by Bircher, Gaylord, Marine and Lenhart *et al.*

McCarrison's experimental production of goiter in man is of particular significance as it took place by the fifteenth day, reaching full development within a month. The relatively short latent period thus observed seems to remove one of the greatest obstacles to acceptance of the infectious theory of goiter on the part of the older authorities, who maintained the disease could not be bacterial on account of the long exposure necessary for its development.

Particularly convincing are the experiments in which fecal bacteria from goitrous individuals were fed pregnant goats who gave birth to cretin kids with large congenital goiters. Goiters were similarly produced in rats. The anërobic intestinal flora were most marked in their goitrigenous action.

McCarrison explains the frequency of cretinic degeneration in rural districts by the lack of hygiene and sanitation in these regions, its prevalence in mountainous and hilly regions by the greater possibility of surface contamination of the water supply through torrential waterfall, the declivity of the terrain, and lack of water supply protected by aqueducts, etc. The geological condition of the land is only of importance on ac-

count of its porosity to water. The greater incidence among farm workers and miners is explained by their contact with infected soil. (MacKenzie.)

McCarrison emphasizes that water pollution *per se* is not the cause of infection, but just as in the case of typhoid fever, water pollution plus the specific excitant of the disease, i. e., fecal bacteria and their toxins.

The greater prevalence of the disease in marshy regions is ascribed to the greater danger of infection through infected water ever present in these areas. According to this view drainage of swampy endemic districts should be followed by a decrease in goiter and cretinism. Such observations, it may be incidentally remarked, have actually been recorded by St. Lager and others.

The relation of a contaminated water supply to the production of goiter in brook trout has been studied by Marine and Lenhart (*c*) and Gaylord. The fish were confined in a series of tanks placed one above the other in a flowing stream harboring normal trout above and below the laboratory station. Stagnant water and unclean tanks produced thyroid hyperplasias among the confined trout in direct ratio to the amount of impurities present. Thus 84 per cent of the fish in the lowermost tank developed goiter under these circumstances, while the upper tank showed but 3 per cent of thyroid hyperplasias. The addition of iodin, mercuric chlorid or arsenic in small amounts, to the water in the tanks, cleaning the same, or the introduction of fresh water led to a decrease in the goitrous tendency. Gaylord administered scraping from the fish tanks to dogs and rats which developed goiters. Boiling rendered this material innocuous.

McCarrison (*c*) has aptly applied these data in conclusions drawn from study of endemic cretinsm in the Indian villages along the Gilgit-Fan River, remarking that the incidence of the disease regularly increased from 12 per cent of the total population in the uppermost to 46 per cent in the lowermost village, which received the accumulated drainage from the six communities lying above it.

McCarrison likewise carried out a number of therapeutic experiments which tend to bear out his contention for the intestinal origin of the disease. Agents such as thymol and other intestinal antiseptics, composite vaccines prepared from intestinal bacteria of goitrous individuals, similar auto-vaccines, or staphylococcus vaccine, lead in many instances to decrease in, or in favorable cases to a disappearance of, the goiters.

The relation of the thyroid to the infectious etiology of endemic cretinism is regarded by McCarrison as an indirect one. In addition to its control of growth and metabolism the thyroid functions in combating toxemia from intestinal and other causes. In the event of the specific excitants of the disease being present there is greater need of functional activity, together with an actual injury of the thyroid tissue. For these reasons, hypertrophy ensues, which is indirectly but favorably influenced by the

amelioration of intestinal toxemia from whatsoever cause, the antiseptic action of thymol, etc.

A critical survey of the accumulated evidence renders it difficult to avoid acceptance of the bacterial theory of McCarrison. True it is, however, that still many facts require confirmation and further elucidation. In particular more exact work is required on the nature of the bacteria and their toxins capable of producing goiter and cretinism. Also further corroboration and elaboration of therapeutic experiments are necessary.

McCarrison rather firmly adheres to the "unitarian" conception of the pathogenesis of the disease so far as the thyroid is concerned, inasmuch as he denies any fundamental difference between endemic or sporadic goiter and cretinism. He stands, however, in an isolated and not easily defensible position in regarding the disease as one of "the thyroid parathyroid apparatus." It would seem to the present writer that the brilliant results of his researches could be better applied in affording an adequate explanation for the "dualistic" conception of the disease (see above) which accepts a noxus affecting all organs and tissues of the body in addition to its early and local effect upon the thyroid gland with resulting hypothyroid symptoms. Indeed, the stumbling-block in the path of acceptance of this conception has remained just the uncertainty as to the causative agent involved. This doubt McCarrison has largely removed. The acceptance of an intestinal toxemia acting slowly upon all organs and tissues, particularly upon the sensitive endocrin and nervous systems, would adequately account for not only the hypothyroid symptoms, but also the early and frequent presence of deaf-mutism, as well as the prominence of idiocy and cardiac symptoms in the cretinic degeneration. The fundamental differences from hypothyroidism shown by the cretinic degeneration as emphasized by European writers, viz., the usual development of the symptoms at a later date, the irregularity of the retardation of the ossification, the absence of parallelism between thyroid pathology and the general symptomatology, also a number of other peculiar characteristics, can be clearly understood with the aid of the bacterial theory. In view of the pathologic findings in the pituitary and other endocrin glands as well as the association of endemic cretinism with endemic tetany, etc., and their existence at times in combination in the same individual, it seems indeed possible that the thyroid is not the only member of the endocrin system involved by the disease. This can be interpreted as further evidence supporting the bacterial theory of the cretinic degeneration.

General Summary of the Etiology of the Cretinic Degeneration

The influence of heredity in the development of the disease is marked. The offspring of parents affected with the cretinic degeneration, particularly goiter, are most liable to contract the disease.

Transmission of the disease through drinking water is a thoroughly established fact. The disease is not produced by dissolved chemicals in the water, nor by radioactivity.

The hydrotelluric theory of Bircher, attributing the disease to deposits in certain geologic strata, also the Plutonian Theory of Répin, are disproven.

The etiologic agent in water collects in the sediment and may be destroyed by boiling, partially removed by filtration; decreased or caused to disappear by general hygienation of the water supply.

Theory of direct contagion: There is considerable evidence, but nearly all of indirect nature, that intimate contact in dwellings and with fomites of affected individuals may cause the disease.

The Bacterial Theory of McCarrison is supported by endemiological, epidemiological, clinical and experimental evidence of importance. It offers a reasonable explanation of the known etiologic data in production of the disease; the influence of the water supply, close contact, the conformation of the soil, etc. It traces the source of the causal agent to animal and human excrement, particularly to intestinal bacteria and their toxins, but further corroboration and elaboration are necessary before general acceptance of this theory can be expected.

Pathology

The Thyroid Gland.—*The Thyroid Gland* of Endemic Cretinism shows no essential pathological lesions differing from those exhibited by this organ in hypothyroidism. Though all grades of thyroid degeneration may be present, the pathological changes in the gland fail to show as definite parallelism with the clinical symptoms as seen by sporadic hypothyroidism. This is particularly exemplified by endemic deaf-mutes and idiots who on postmortem may occasionally possess glands with only insignificant lesions. The most acceptable explanation for this discrepancy is the theory that the cretinic degeneration is due to a toxemia affecting directly various organs in addition to the thyroid. The pathological changes may be hypertrophic (goiter) or atrophic in type.

a. **Pathogenesis of Goiter.**—Thyroid hypertrophy (endemic goiter) may be the only demonstrable manifestation of the Cretinic Degeneration. Goiter is much more prevalent among endemic than sporadic cretins, Ewald reporting thyroid hypertrophy in 62 per cent of endemic cretins. According to the chemopathologic standpoint adopted by a number of modern investigators of thyroid disease, all forms of thyroid hyperplasia are essentially due to toxic injury and consequent subfunctionation or increased need for the thyroid hormone over and above the output capacity of a given normal gland. In this regard Marine and Lenhart (*g*) remark:

"Seventy-five per cent of all cretins have clinically enlarged thyroids, and, if careful anatomical examinations could be made before the clinical manifestations of cretinism supervened, there can be little doubt that a well-marked active hyperplasia would be found in all cases in which thyroid tissue was present. It would thus seem that the same nutritional deficiency or disturbance which causes the thyroid cells at first to grow and divide, later causes their death when their work and growth energy is exhausted. This process is more evident in myxedema in which the age of the individual allows earlier detection through more careful observations during the early or developmental stage. The colloid is practically absent. The epithelial cells have lost their regular and uniform columnar type characteristic of the early state of active hyperplasia and are irregular in size and shape. There is perhaps some piling up of the epithelial cells and desquamation of the partially degenerated cells. The nuclei are in general large, often hyperchromatic and irregular in size and outline. Nuclear figures are still observed, but the new formation of cells is not sufficient to offset the cell-death, and the follicles become smaller, though still preserving the infoldings of well developed hyperplasia. The surrounding fibrous stroma is relatively, perhaps absolutely, increased, and as the follicles become smaller from the death of their secreting cells the fibrous bands appear wider, and finally give the appearance of a generalized cirrhosis in which are nests of compressed epithelial cells with or without the outlines of follicles. This interstitial cirrhosis is secondary to and consequent on the death of the epithelial elements. Lymphoid foci are scattered here and there throughout the stroma. This is the simplest picture of the anatomical changes in the thyroid in myxedema, and those occurring in the cretin thyroid are similar. Most cases, either of myxedema or cretinism, in man do not present so simple an anatomical picture for the reason that other processes as cyst formation, hemorrhage, calcification, adenoma, groups of enlarged follicles filled with desiccated colloid, etc., may all be crowded into the same gland."

"Summing up, then, the type of atrophy supervening on active hyperplasias and clinically associated with myxedema or cretinism is a cell-death due to exhaustion from overwork and malnutrition. The process is simple, but the anatomical changes in such glands, especially in long-standing cases, are often highly complex."

This standpoint is supported by a chain of evidence as follows: The observation of Wilson and Kendall of the small amount of active iodin in thyroid adenomata, the demonstration of Marine and Lenhart (*c*) of the decrease in the amount of iodin in the gland immediately preceding the hyperplastic changes, the parallelism of the degree of cellular increase with the degree and duration of the iodin diminution, the inverse ratio existing between the iodin content and amount of hyperplasia and finally the

absolute chemical identification of the iodin as a large part (over 60 per cent) of the molecule of the thyroid hormone (Kendall (*i*)). *It may therefore be regarded as probable almost to the point of actual demonstration that thyroid hyperplasia and hypertrophy is a compensatory and not an idiopathic process requiring highly theoretical hypotheses for its explanation.* According to Marine and Lenhart's important investigations there may ensue during the early phases of hyperplasia a *quantitative increase* of thyroid hormone secretion into the blood stream which, however, merely compensates for the *decreased qualitative efficiency* of the same. *From this new viewpoint, all thyroid hyperplasias except the physiological* (goiter of pregnancy, etc.), *indicate decreased thyroid function per integral unit of the thyroid gland.*

Thus we are faced with a new conception of thyroid pathology which is diametrically opposed to Möbius and Kocher's original conception of hyperthyroidism as the antithesis of hypothyroidism. A discussion of the hyperfunctional theory of exophthalmic goiter lies beyond the limits of the present treatise. It may suffice to state that there are grave objections to this viewpoint, also that the hypertrophy of the gland in thyrotoxicosis may with propriety be accounted for by a subfunctional or dysfunctional hypothesis. (See the excellent discussion of the pathogenic theories of Graves' disease by C. P. Howard in a chapter of the present work.)

Hypertrophy and hyperplasia of the gland is, as stated, the primary reaction to the toxic agent. According to McCarrison (*a*), the first changes include an increase in height of the vesicular epithelium, increase in the number of vesicular and parenchyma cells, formation of new vesicles. The vessels become enlarged and congested, the colloid is absorbed, the multiplying cells show unusual variations in size and shape, also mitotic figures. The vesicles become irregular in outline. An increase in fibrous stroma and lymphoid cells ensues. This process is both compensatory and of a chronic inflammatory nature. If now the toxic causative agent abates, the colloid goiter develops. Growth ceases and colloid is again stored up. True colloid glands are "physiologically normal and anatomically abnormal" (Marine and Lenhart). They are distinguished from normal glands only by their size and their showing signs of previous hypertrophy. Individuals with such thyroids do not develop hypothyroid signs and symptoms, but such may have appeared previously.

If, however, the original toxic agent continues its action, the harmless colloid goiter just mentioned may fail to develop and the hyperplastic processes become overshadowed by the atrophic. A colloid goiter at first fully compensated as to function may on further toxic or infectious insult, secondarily, lose much of its functionating tissue and hypothyroidism result (goitrously degenerated thyroids of cretins). Goiters are subject to various retrogressive processes, including cloudy swelling, hyaline, cal-

careous, amyloid, parenchymatous and fatty. Hemorrhage and cyst formation may occur. These changes may or may not be accompanied by the systemic effects of thyroid subfunction.

b. **Atrophic Thyroid Lesions in the Cretinic Degeneration.**—The thyroid gland is occasionally reported absent in endemic cretinism. (Kocher (*b*), Langhans (*c*).) Wagner von Jauregg rightfully raises the point whether or no sporadic athyreosis occurring in endemic cretin areas might not account for such absent thyroid glands, and also points out that the absence of the thyroid in endemic cretins has not been proven beyond the possibility of objection, i. e., by complete histological examination of the cervical tissues.

Hanau, De Coulon, Bayon, S. Getzowa, Langnans, E. Bircher (*d*), McCarrison *et al.* have examined the thyroid histologically. The lesions found include great decrease in the normal acini fibrous tissue overgrowth, some of which may show hyaline degeneration (Bayon, Getzowa). Schlagenhaufer and von Wagner carefully studied the thyroid of an endemic cretin four years of age. Macroscopically the gland was normal. The glandular epithelium showed, however, severe lesions. The cells were of irregular size and poorly demarcated, the protoplasm stained irregularly, the nuclear membrane was thickened, the nuclei swollen and variously degenerated.

Other ductless glands may be affected in endemic cretinism. Though usually reported negative (E. Bircher, Getzowa, Scholz), the parathyroids were not found in a case of nervous cretinism showing tetany (McCarrison (*a*)). The close association of endemic tetany to endemic cretinism would also suggest the liability of both the thyroid and parathyroid being affected by the same toxic agent. *The pituitary gland* according to Shönemann is the seat of pathologic changes in 95 of 112 cases without goiter. All but one of the goitrous cases had abnormal pituitary glands. Among the histologic changes were connective tissue overgrowth, hyaline degeneration, colloid formation, vascular and chromophilic hyperplasias. De Coulon reported macroscopic hypertrophy but diminution of the glandular tissue. B. and A. Nièpce report similar lesions.

The *skin* is less frequently myxedemic than in sporadic cretinism though McCarrison's Indian cretins often exhibit swollen integuments. There are but fragmentary observations in the literature of the character of the histologic lesions. Bernard and Wagner v. Jauregg found no characteristic changes.

The Central Nervous System is attacked with characteristic severity. Findings at autopsy include thickened and adherent meninges, inequality in size of the hemispheres, disproportionate smallness of the cerebellum, imperfect convolutions, preponderance of the gray matter, internal hydrocephalus, increased resistance on section. Typical histological findings have not been reported. Extensive cord changes were noted by McCar-

rison in his autopsy of an endemic cretin with spastic diplegia. Additional pathological study of endemic cretinism is indicated.

Marked disturbances in the special senses are frequently met with. Speech may be affected rarely *per se,* more frequently in combination with deaf-mutism where it may be secondary to the failure of hearing spoken language. The power of articulation may be inhibited through failure in development of the cortical center or higher psychic centers in endemic idiocy (Scholz and Zingerle), or peripherally through thickening of the vocal cords and pharyngeal anomalies.

With regard to the *acoustic organs,* Falta (*a*) has succinctly stated the present status of knowledge and is therefore quoted as follows:

"The statements as to the functional disturbances or the pathologico-anatomical findings in the deaf cretins and in the endemic deaf-mutes diverge greatly. Hammerschlag, whom we have to thank for the first exact investigations, found on the one hand alterations in the peripheral hearing apparatus, and on the other only disturbance of the perception of sound, as also found Scholz, Fröschel, and others. Further, there was found in endemic cretinism incomplete ossification of the stapes, inhibition of development of the epithelial cells in the ductus cochlearis (Habermann, Alexander), shortening of the base of the skull and thereby disturbance in the development of the organ of hearing (Danzinger, Bircher), incomplete ossification of the organ of hearing with hyperostotic growths at other places (Moos and Steinbrügge). Anomalies of the malleus (Nager), myxedematous thickening of the tympanic mucous membrane, etc., have been regarded as the cause of hardness-of-hearing. Recently, E. Bircher has strenuously criticised a portion of these findings or their significance. To-day we may safely assume that we may ascribe great importance to the degeneration in the cortical centers or the developmental inhibitions in the cortical centers, and that the different alterations are directly elicited by the goiter noxus and are coördinated with an insufficiency of the thyroid, which finally sets in (Pineles)."

It should, however, be mentioned that B. Nièpce found definite pathological changes in the acoustic nerve in several cases.

The *internal organs* have been little studied.

The *cardiovascular system* may undergo atheromatous changes with cardiac lesions. (See section Symptomatology.)

Sexual retardation corresponds in general to that observed in sporadic hypothyroidism. In light cases the power of reproduction may be retained. The *libido sexualis* is weak or absent in the severely affected, whose reproductive organs may remain infantile. Cretins seldom conceive. When this does occur the fetuses are born dead (E. Bircher, Eppinger). McCarrison has made the same observation in the case of goitrous goats. The female generative organs show developmental retardation and microcystic

degeneration. Langhans reported in a cretin of 24 years the testes and epididymus of child-like size, spermatozoa in diminished numbers or lacking altogether.

The Osseous System. The retardation in development of the skeleton resembles in the main that of sporadic hypothyroidism but there are certain minor differences. The epiphyseal closures are markedly delayed but not to such a great degree as in severe hypothyroidism of sporadic nature. (Langhans, von Wyss, etc.) But according to Breus and Kolisko, also E. Bircher (*b*), the retardation of epiphyseal union is only exhibited during the years of normal growth. After the thirtieth year the epiphyses are closed in most cases. In this we have a fundamental difference from sporadic hypothyroidism in which the untreated cases of severe type exhibit open epiphyses until advanced age. Later authors emphasize the irregularity of the ossification and its retardation. In certain bones these changes are marked, others escape again in contrast to non-endemic cretinism. It is also to be remarked that in the early years of life, the retardation of bone formation is very slight on account of a certain period of exposure seemingly necessary for development of the disease. This behavior Dieterle (*b*) contrasts with sporadic athyreosis in which wide open fontanelles and epiphyses persist from babyhood. Cranial measurements have been carried out by v. Scholz (*b*), E. Bircher, Höfler, B. Nièpce, *et al.* The skull of endemic cretins is characterized by the short *basis cranii,* the great breadth of the interorbital septum and the abnormally low superior maxillary bone. The horizontal circumference is normal but the skull is both brachycephalic and platycephalic. Many of the older observations on the cretin skeleton are of little value on account of confusion with other growth anomalies. As an example may be mentioned the classical error of Virchow, who accredited the cretin skull with an early tendency to synostosis, having mistakenly so described cases of chondrodystrophy. From a study of the literature striking differences in the cranial conformation of endemic and sporadic cretinism do not, however, seem to be apparent.

The *metabolism of endemic cretins* has been little studied as yet. It presents an attractive field for research. What little is known suggests a similarity to that of sporadic hypothyroidism. Scholz's (*a*) earlier researches were carried out in part with questionable methods but indicate a lowered excretion of protein and protein metabolites including uric acid, creatinin, urea, ammonia and sulphuric acid. Scholz states that an increased protein elimination is not so easily obtained through the administration of thyroid substance in endemic cretinism as in myxedema. This may be explained etiologically by the fact that not all the pathological changes in the cretinic degeneration are definitely describable to a defectively functionating thyroid gland. It would seem to the author that a study of the basal metabolism might be especially applicable in differen-

tiating those cases in which the hypothyroid factor is marked and thus enable a proper selection of cases for thyroid therapy.

Symptomatology

The clinical expressions are so varied that it was long before it became generally recognized that endemic goiter, cretinism, idiocy, goiter-heart and deaf-mutism belong to a single nosological entity. Even at present, endemic goiter is occasionally still described as a disease *sui generis*. This has in part come about through the prominence of this symptom but also because an outbreak of goiter may be the only manifestation of the disease in lightly affected areas. As the endemic increases, however, very gradually cretins, deaf-mutes and idiots begin to put in an appearance though never in numbers approaching those affected with goiter. As has been emphasized by many writers, cretins are usually born of goitrous parents. There is no necessarily sharp demarcation between the various forms of the disease which merge into each other. Besides the typical clinical pictures, many slight bodily and mental abnormalities occur in endemic areas which careful observers are prone to consider likewise manifestations of the disease. Among such may be included certain characteristics frequently regarded as radical and familial by the laity, viz., small statures, disproportionate development, ugly features, lack of ambition, quarrelsomness, and the like.

Griesinger quoted by Crotti aptly remarks in this regard, "Where the endemic is very severe, the entire population is affected. Besides the true cretins, the half-cretins, and goiter-bearers, there are innumerable weak-minded, miserable and badly proportioned individuals; there are many deaf-mutes, stutterers and stammerers and strabismus and deafness are frequent. Through the entire native population runs a streak of physical degeneration and mental dullness; even those individuals who pass for healthy and intelligent are, on the whole, unlovely, narrow-minded and sluggish and the country teems with mean-spirited philistines in whom the qualities of heart are insufficient to compensate for the lack of intellect."

The clinical symptoms and signs of cretinic degeneration may in certain cases or epidemics be indistinguishable from those of sporadic cretinism. In many descriptions this fact is but more clearly emphasized by the forced attempts of the authors to bring out differential points. It should be emphasized that the thyroid factor differs in various epidemics. Some are characterized by greater numbers of typical hypothyroid cases and cretins than others. The latter are less amenable to treatment than the former. This has been the cause of much confusion. For the sake of brevity, the reader is referred to the section on the symptoms of hypothyroidism for a detailed description of such clinical manifestations. The

following remarks are limited to the distinguishing features of cretinic degeneration.

This endemic disease is characterized by its multiformity whereas all sporadic cretins bear a general resemblance to one another. Endemic cretins correspond to no fixed type. A visit to the endemic areas of Switzerland or Austria, or observation of the photographs of groups of endemic cretins clearly demonstrate this. It may be mentioned that the following characteristics are usually present: a pale or pasty complexion, a stupid or sullen facial expression, the root of the nose retracted, a large tongue and a short neck. The growth is stunted but in general less so than in sporadic hypothyroidism. The skeletal changes are distinguished by their irregularity and lack of symmetry (see Pathology) and are usually not proportional to the severity of the mental and other symptoms. Breus and Kolisko call attention to the shortening of the upper extremities. A disproportionate length of trunk as compared to the limbs is frequent.

The Thyroid Gland.—*Goiter.*—The thyroid gland undergoes hypertrophic or atrophic changes in the cretinic degeneration. The former give rise to endemic goiter, a very common manifestation of the disease. The atrophic glands are the cause of the lean necks with prominent sterno-cleido-mastoid muscles and larynx that are met with in high-grade cretins. A *goiter* may be the only sign of the cretinic degeneration. In certain affected areas, notably those in the United States, this holds quite true. Goiters are much more prevalent among endemic than sporadic cretins. Among Osler's American sporadic cretins, 12 per cent showed goiters. Among McCarrison's endemic cretins, 40 per cent were goitrous. In certain communities, endemic goiter becomes so frequent that practically all the inhabitants, as well as domestic animals, are affected.

Although endemic goiters are in the great majority of cases eminently chronic, they may develop acutely in newcomers to a goitrous locality ("acute" or "summer goiters"). The degree of enlargement is very variable. It may be so slight as to remain unnoticed by the patient, become the usually moderate cervical enlargement, or rarely develop into an enormous growth lying on the anterior surface of the chest reaching downward even to the waist. With regard to the anatomical location, thyroid tissue, wherever located, may become goitrous. Thus submaxillary and lingual and intralaryngeal goiters are known. The substernal type is of especial surgical importance. The neck may show no enlargement in such cases. For further details surgical works may be referred to.

Pressure symptoms due to goiter often occur when the growth is large. Of Krönlein's 191 patients 62 gave a history of paroxysmal dyspnea. Congestion of the face and neck is common in goitrous individuals due to venous compression, respiratory embarrassment or goiter heart. The trachea may become compressed particularly by the intrathoracic type. Consequent to this compression may develop stridor, dyspnea, tracheo-

bronchial catarrh and cough. The so-called "goiter asthma" usually comes on at night, is characterized by profound dyspnea and may end fatally. It may be induced by pressure on the recurrent laryngeal nerves. Woelfler reported paralysis of vocal cords in 10 per cent of his series, Krönlein, vocal disturbances in 62 of his 191 cases. Other cranial and spinal nerves are rarely compressed giving corresponding symptoms, especially pain in head and neck. Dysphagia is most common. Goiter heart of the respiratory type may develop.

Bacterial inflammations of goiters may ensue after trauma or treatment by injections resulting in acute thyroiditis, even necrosis and gangrene.

Myxedema, even in older subjects, is generally less commonly present than in sporadic hypothyroidism. According to Bircher, 60 per cent of endemic cretins do not exhibit myxedema. This, as do all the clinical features, appears to differ in different localities and epidemics. Scholz found it rarely among Steiermark cretins; v. Kutschera frequently in his series; McCarrison in his Indian cases describes a myxedematous type of endemic cretinism.

Anomalies of dentition and the jaws are described by Kranz, who failed to find similar changes in thyroidectomized animals and described them therefore as characteristic of cretinic degeneration. In spite, however, of this experimental evidence similar lesions, delayed and irregular dentition, hypoplasia, defective enamel, and liability to wear down prematurely, are characteristic hypothyroid symptoms.

The *nervous system* suffers more severely and sometimes more frequently than in sporadic hypothyroidism. This is evinced by the great prevalence of idiocy and feeble-mindedness in endemic localities. Quite characteristic is the development of idiocy without accompanying marked subthyroid stigmata such as always occur when the mentality is severely affected in sporadic cretinism. On the contrary, the body may be greatly stunted showing various degenerative changes and yet the mentality be but slightly affected, an excellent example of the multiformity of the clinical picture. Physical defects, however, are usually present to a certain degree.

A peculiar type of cretinism with cord symptoms has been described by McCarrison in India and later by Crookshank in England. It is not known in America. The following is taken from McCarrison (*a*), who describes it as:

"A condition of cretinous idiocy with associated cerebral diplegia and tetany due to congenital fibrosis of the thyroid and parathyroid gland. One third of all cretins in endemic localities of the Himalayas belong to this type." Such afflicted children are helpless and of defective mentality. There may be nystagmus and strabismus and facial grimaces. The knee jerks are increased, the spasticity may be so great that affected in-

dividuals may walk on their toes. The lower limbs are most often the seat of the spastic diplegia. Sensitivity of the skin is present. The upper limbs may show tetanoid movements and the characteristic flexed thumb of tetany. Myxedema may be present. Improvement occurred on thyroid therapy.

Deaf-mutism is disastrously prevalent in association with cretinic degeneration. This seems particularly true of Switzerland and Austria. In the former country the ratio, according to St. Lager, is 5 cretins to 4 deaf-mutes. Bircher who has given this subject special attention claims that 80 per cent of all deaf-mutes in Switzerland are ascribable to cretinic degeneration. In Austria, Scholz found 61 per cent of his series hard of hearing or deaf-mutes. In India the proportion is greater, 87 per cent (McCarrison). Where endemic cretinism flourishes, endemic deaf-mutism is to be found and there only. This holds true so universally as to clearly indicate that both are but manifestations of the one disease, the cretinic degeneration. This interrelationship and the great frequency of deaf-mutism are clearly shown by the Austrian Sanitary statistics of 1900. In the entire country there were together 17,286 cretins and 27,-567 deaf-mutes; 64 cretins and 100 deaf-mutes per 100,000 inhabitants. However, in the regions where cretins were most numerous, deaf-mutes were present in like ratio. Thus Salzberg, Steiermark and Carinthia were found to have respectively 179, 175 and 226 cretins, and 133, 139 and 182 deaf-mutes per 100,000. Conversely in Dalmatia, Istria and Bukovina there were enumerated only 7, 42, 32 cretins and 66, 96, 85 deaf-mutes per 100,000.

Deaf-mutism may exhibit itself as practically the only stigma of this degenerative disease. Again, it may be associated with hypothyroid symptoms and may, at least to a large degree, be dependent upon loss of thyroid function. The intelligence may at times be remarkably good in the presence of deaf-mutism. Usually the contrary holds true. Speech, even when no pathological defect is present, remains undeveloped if no hearing be possible. On the other hand, hearing may be excellent but intelligence and speech deficient.

Goiter Heart.—Cardiovascular disturbances are known to be quite frequent among endemic cretins and goitrous individuals. According to Schranz, who studied several hundred goitrous school children and adults, also over 200 autopsy records in Innsbruck, 23 per cent of the goitrous children and 49 per cent of the goitrous adults were found to have cardiac lesions associated with goiters. Cases of valvular heart disease were omitted. In spite of all criticism which tends to reduce the number of these cardiac cases, Schranz's work definitely established the prevalence of cardiac disease in the cretinic degeneration.

In older writings this coincidence of cardiac disturbances with goiter has been frequently the subject of clinical comment. The term *"goiter-*

heart" thus came into use. This appellation in common with so many others in thyroid terminology has been vaguely applied to describe the cardiac changes in thyrotoxicosis as well as in hypothyroidism. The following remarks apply to cardiac lesions in the latter condition. There seems no essential difference between the cardiac lesions of sporadic hypothyroidism and the cretinic degeneration.

Mitral insufficiency, which is not infrequent in these cases, may be due to the hypertrophy and flabby myocardium, less frequently to vegetations of the mitral valve. The right heart may undergo dilatation and insufficiency (Rose's goiter heart) due to the congestion in the pulmonary circulation. Mechanical factors resulting from the weight and pressure of a large goiter may embarrass the circulation and lead to the "pneumonic" type of goiter-heart described by Kocher. It is certain, however, that the mechanical factors in the development of cardiac lesions are of much less importance than degenerations of the heart muscle.

As to the *Hematology* of cretinic degeneration, the only available data seem those of McCarrison (*a*) who reports among 73 cases of endemic goiter a decrease in the polymorphonuclear elements in 98.9 per cent of cases, latest increase in the small mononuclear lymphocytes in 92.5 per cent, eosinophilia in 88 per cent and mononucleosis in 23 per cent. Endemic goiter is, however, the lightest manifestation of the endemic disease under discussion. It seems then possible that the leucocytic formula of endemic cretins might correspond more fully to sporadic hypothyroidism, particularly in the more constant presence of mononucleosis. A certain degree of anemia is common in endemic cretinism.

Diagnosis

The most important single factor in the differentiation of cretinic degeneration from other conditions is its endemicity. In the absence of cretinism and deaf-mutism, the occurrence of unusual numbers of goiters suggests the development of the endemic disease. Sporadic cretinism, however, may occur rarely in an area of endemic goiter. Simple goiters are distinguished by small size, occurrence at puberty, during pregnancy, etc.

For reasons already given, the diagnosis from sporadic hypothyroidism may be impossible. Endemic cretinism is distinguished by the following symptoms: the endemicity, frequency of struma, greater involvement of the central nervous system, particularly the mentality, slighter and disproportionate retardation of the ossification and in general the lack of uniformity in the clinical picture. The failure of the thyroid therapy in some cases and the low tolerance to thyroid substance are further points of differential value.

It is probable that in endemic areas other growth and developmental dystrophies such as true nanism, infantilism, mongolism are frequently mistaken for cretinic degeneration. The differentiation of these conditions has been already detailed. (See Diagnosis of Hypothyroidism.)

Treatment

Prophylaxis.—In view of the increased importance recently attached to the toxemic and bacterial causation of the cretinic degeneration, new impetus should be given to the prevention of the disease by means of hygienic measures. It is indeed remarkable that hitherto no general attention has been given by public and private health authorities to such prophylaxis in this widespread disease. Excellent proof has long been afforded of the value of the preventive treatment. Though rather refractive to therapeutic measures, endemic goiter and cretinism will, in all probability, be soon generally regarded as preventable diseases. The chemical composition of the water is chiefly of importance as affecting its general hygienic qualities. The main point to be observed is the avoidance of surface contamination, particularly fecal. In view of recent experiments already quoted, it is recommended to boil or chlorinate a dubious water supply. It is an established fact that certain natural waters prevent or alleviate cretinic degeneration, especially goiter. Such waters are bacteriologically pure and have a high iodin content.

The experimental production of goiter and cretinism by the alimentary introduction of fecal material from affected individuals, also by bacteria, (McCarrison) emphasize the important rôle probably played by soil contamination in producing the disease. This writer therefore advises the strictest care as to sewage disposal in endemic areas, including the removal of stables and barnyards from the vicinity of houses, the filling in of cesspools, introduction of sanitary plumbing, as well as greater attention to personal hygiene. It would seem that about the same measures so well applied in stamping out a typhoid fever epidemic might be instituted. Removal from an endemic area often effectually prevents an outbreak of the disease. It may be kept in mind that patients who have been apparently cured still remain prone to a recurrence of the disease, particularly on a return to endemic areas.

Many examples of the therapeutic effect of the introduction of a pure water supply are cited in the literature. One of the most striking is described by E. Bircher. In the village of Asp, there were in 1863 among the population 34 per cent goitrous, 15 per cent deaf-mutes and 8 per cent cretins. In 1907, the upper part of the village obtained a new and pure water supply, while in the lower the old system remained. In 1910 the statistics gave the following results. Upper village 6.4 per cent goiter dis-

tributed among 8 per cent adults and 5 per cent school children. Lower village 38 per cent goiter among 20 per cent adults and 66 per cent school children. For other instances, see section Etiology.

Treatment of Goiter.—The *preventive treatment* includes a general observance of personal hygiene, a proper diet, and wholesome mental surroundings. In view of recent experimental work connecting endemic goiter with an infected water supply and bacterial absorption from the intestine, it is likely that the same etiological factors may play a rôle in sporadically occurring thyroid hypertrophies. Therefore, pure water, pure food and proper care of gastro-intestinal diseases, especially chronic intestinal stasis and colitis, be they present, should be included in the prophylaxis against goiter.

The avoidance of tight neck-bands and occupations requiring stooping, therefore congestion of head and neck, is recommended.

The influence of the use of sea-salt in the prophylaxis of goiter has been emphasized by L. Taussig *et al.*, who comments upon the freedom of the disease among seacoast dwellers and other communities in which sea salt is used extensively. It is suggested that such means of prevention be employed in goitrous communities. The therapeutic action depends not upon the sodium chlorid but rather upon the small amounts of iodin originating from pelagic flora. It may be recalled that goiter and cretinism among animals has been likewise prevented and benefited.

Recently the prevention of goiter on a large scale in the schools has been accomplished by O. P. Kimball and D. Marine (*b*) through small doses of iodin preparations (0.2 to 0.4 gm. sodium iodid daily). The results may be quoted as follows:

"Not a single pupil in whom the thyroid was normal last year and who took iodin, showed any enlargement, while of those not taking iodin, 26 per cent showed definitely enlarged thyroids—some moderately large goiters. Even more than a prophylactic action is shown in the results—just one-third of the goiters marked "small goiters" disappeared; and one-third of those marked "moderate goiters" showed a decrease of 2 cm. or more. Accordingly a distinct therapeutic effect is clearly demonstrated."

Iodin has been known for centuries in the treatment of goiter. It may be used externally as the tincture or in an ointment and is often very effective in small, recent, or congested hypertrophic glands. Usually, however, internal treatment is required. Dock recommends 0.1 to 0.2 gm. (1.5 to 3 gr.) of iodin daily in the form of Lugol's solution. It is probable that iodin thus administered stimulates the thyroid to increase its hormone output by supplying increased amounts of the chief element of thyroxin (containing 65 per cent iodin, Kendall), the active constituent of the gland. This would explain the good results obtained by the use of

thyroid extract in simple thyroid adenomata. Probably a standardized dosage of thyroxin will become the medical treatment of choice in future.

Various intestinal antiseptics have been recommended by McCarrison in the treatment of endemic goiter. (See same below.) It would seem favorable from the results achieved to make a trial of this treatment combined with dietary measures.

Röentgenological treatment properly controlled may be recommended before resorting to surgery.

The mortality of thyroidectomy has now been so reduced in skillful hands that selected cases may be advised operation with propriety. Very large, cystic, indurated or calcified goiters do not yield to medical treatment. In such instances or when pressure symptoms intervene, surgery is indicated. Great improvement in the operation of thyroidectomy has been made since Kocher's development of the operation by Halsted, C. H. Mayo, Crotti and other operators. The mortality in skilled hands is low. It is well, however, to bear in mind that postoperative *cachexia strumipriva* is still met with. Such postoperative hypothyroidism usually develops so slowly that it frequently escapes the observation of the attending surgeon and fails to be noted in surgical statistics. One of the interesting facts brought out by recent basal metabolism studies is the detection of greater numbers of such cases, particularly those of a mild type. In spite therefore of the splendid results of modern thyroid surgery, it seems justifiable in all suitable goiter cases to try the effect of medical treatment before recourse to thyroidectomy.

Thyroid Treatment of the Cretinic Degeneration.—Thyroid therapy is productive of less certain results in the cretinic degeneration than in in sporadic hypothyroidism. This may be fairly expected in view of the general character of the disease. The more typical hypothyroidism is developed, the better results can be expected. It is likely that failure to properly select and control the cases together with the uncertain quality of the thyroid preparations then in use were responsible for the statements in the older literature as to the inefficiency of thyroid therapy in cretinic degeneration. In many instances the results of treatment have been satisfactory. Thus v. Kutschera (a), who carried out this mode of treatment on a large scale in Austria, reported in a series of 1011 endemic cretins marked improvement in 42.8 per cent, definite improvement in 48.6 per cent. A small minority failed to be benefited. High-grade idiots and deaf-mutes were excluded from this series. It is unfortunately just such individuals who are least benefited by thyroid treatment. In these instances, atrophic and sclerotic processes have determined actual irreplaceable tissue loss, as the thyroid factor is small or perhaps at times entirely absent. For thyroid preparations and dosage, see section Treatment of Hypothyroidism.

No comprehensive reports of the control of treatment of cretinic degeneration by basal metabolism determinations are known to the writer.

Such a procedure might give much aid in the selection of cases as well as the control of treatment.

Treatment With Aid of Intestinal Antiseptics.—McCarrison (*a*) warmly recommends full doses of the intestinal antiseptics, such as iodin, β-naphthol, quinin, thymol, salol, and reproduces a number of photographs showing improvement after such treatment which was carried out in 200 cases. Messerli of Lausanne has confirmed McCarrison's experience with the use of intestinal antiseptics including the use of salol and creosote. The latter writer claims good results in some cases with the use of autogenous vaccines of fecal bacteria. If intestinal toxemia should on further research be demonstrated as an important cause of the cretinic degeneration, the modern dietetic treatment of this condition might become an important adjunct to the care of such cases.

Tests for Thyroid Disorders . . . . . *Emil Goetsch*

Introduction—The Epinephrin Hypersensitiveness Test (Goetsch) for Hyperthyroidism—Basal Metabolism Determinations—Uses of Metabolic Rate Test—The Hyperglycemia Test—Carbohydrate Tolerance in Experimental and Clinical Hyperthyroidism—The Specific Ferment Test of Abderhalden—The Aceto-Nitrile Test of Reid Hunt—The Test of Claude, Baudouin and Porak—Marinesco-Rosco Complement Deviation Test—Therapeutic Test with Iodin and Thyroid Extract—Epinephrin Mydriasis Test of Loewi.

The Thyroid Gland and Its Diseases

Clinical Syndromes

Tests for Thyroid Disorders

EMIL GOETSCH

BROOKLYN

Introduction

The importance of having specific clinical tests as aids in the diagnosis and differentiation of that large and obscure group of diseases due to disorders of the endocrin glands is apparent. Of all the ductless glands the active principle or the specific secretion of the thyroid gland is perhaps the best understood. The clinical evidences of over- or under-activity of the thyroid have been known and recognized for a considerable time, and more recently great strides have been made in our knowledge concerning the physiological effects of thyroid secretion. It is desirable to know what the properties of the specific secretion of a gland are and what the clinical manifestations most likely would be if this secretion be present in excessive or diminished amounts, before we can hope to apply a clinical test for disturbances in the function of a gland, and hence in the character and amount of its secretion. It was not long after we learned of the action of thyroid secretion that tests for evidences of its presence in increased or diminished amounts were forthcoming, and subsequently served as aids in the recognition of clinical states of hypo- or hyperthyroidism.

There is a great deal of evidence now available which indicates that thyroid secretion has at least three very definite functions upon which are based three of the recent and most valuable tests for thyroid disorders. Some of the older, less practical and hence less valuable tests were doubtless in several instances based upon these same facts, although the underlying explanation was not recognized. In the first place we know that thyroid secretion has a specific stimulating action upon the sympathetic portion of the autonomic nervous system rendering the latter

hypersensitive to the action of epinephrin. It is upon this fact that the epinephrin hypersensitiveness test devised by Goetsch is based, and has been recommended by him in the diagnosis of clinical states of hypo- and hyper-thyroidism. Secondly, during the past twenty-five years abundant evidence has accumulated to show that thyroid secretion has an additional stimulating action upon metabolic processes causing, when present in excessive amounts, increased metabolism and when present in diminished amounts, decreased metabolism. It is due to these facts that the determination of the metabolic rate may be used as an index of the presence of an excessive or diminished amount of thyroid secretion. Thirdly, thyroid secretion has a definite action upon the mobilization of carbohydrates, particularly in the liver, and a retarding action upon the combustion of sugar in the blood as a result of which hyperglycemia follows when this secretion is present in increased amounts. As a consequence the determination of blood sugar or, in other words, the test for hyperglycemia has been used as corroborative evidence of an increased or diminished thyroid activity. These three tests are at the present time the most practical and the most helpful.

It may be advisable, however, to outline briefly the older tests of historical interest which are occasionally still used, but which have not proved to be of very great practical help. They have, however, a confirmatory value. Of the three tests mentioned, the first two, namely, the epinephrin hypersensitiveness test and the basal metabolism test are those that have proved to be of definite clinical value, and have come into very general use. The blood sugar determinations or hyperglycemia tests are valuable but of no specific diagnostic importance in thyroid disorders since carbohydrate metabolism is so closely related to the function of practically all of the ductless glands and is disturbed in a relatively large number of unrelated diseases. The action of thyroid secretion upon carbohydrates is not specific to this secretion, hence the disturbance in carbohydrate metabolism is not at all restricted to disorders of the thyroid. Fortunately for the first test, we know of no other endocrin gland than the thyroid, which has a significant stimulating action upon the sympathetic system. In other words, this is a specific action characteristic of this gland. Thyroid intoxication, according to available evidence, is the commonest cause of hyperirritability of the sympathetic system to the action of epinephrin, although perhaps not the only cause. The hyperirritability of the sympathetic to epinephrin in a few conditions other than thyroid intoxications is characterized by a response different from that seen in hyperthyroidism, thus aiding materially in the differentiation. Furthermore, in support of the second test we have the fact that there is no gland which has such a powerful stimulating action as the thyroid upon metabolism. The pituitary gland possesses it in a much less degree and is not so apt to be confused in its clinical disorders with the thyroid.

The Epinephrin Hypersensitiveness Test (Goetsch) for Hyperthyroidism

It has been shown as a result of abundant physiological research by a number of investigators, such as Eppinger, Falta, Rudinger and Hess of the Viennese School, by Asher and Flack (*a*) in Berne, and by Cannon and Levy in this country, that in hyperthyroidism experimentally produced and in a few instances of clinical hyperthyroidism, the sympathetic nervous system is hypersensitive to epinephrin chlorid, and in states of clinical hypothyroidism or after thyroidectomy in animals there is an increased tolerance to injections of epinephrin. Applying this knowledge to a study of approximately 500 patients suffering with disorders of the thyroid gland, it was found by Goetsch (*b*) (*c*) (1918, 1920) that the patients with hyperthyroidism [1] uniformly showed a remarkable sensitiveness to small doses of epinephrin subcutaneously administered. This hypersensitiveness usually expressed itself in rather marked increase of blood pressure and pulse and in exacerbation of the clinical signs and symptoms characteristic of the disease. All cases of hyperthyroidism, whether produced by exophthalmic goiter, adenoma, puberty hypertrophy and hyperplasia or diffuse adenomatosis of the thyroid gland, were verified by careful histological study of all the operative material with especial reference to the occurrence of mitochondria as criteria of functional activity (Goetsch (*a*), 1916). As a result of studies by Goetsch (*b*) (*c*) (*d*) on this subject a clinical test for hyperthyroidism was evolved. This test always confirms and usually establishes the diagnosis of hyperthyroidism. When positive the test is an indicator of hypersensitiveness of the sympathetic nervous system. There is a small percentage of clinical conditions which give a more or less positive reaction, and which are not dependent upon definite pathological change in the thyroid gland. However, the test is positive in all cases of hyperthyroidism. Furthermore, of all the diseases which may possibly be associated with a hypersensitive sympathetic, hyperthyroidism is by all odds the most common. In the presence of a negative response to the test one can state definitely that hyperthyroidism is not present. To be able to differentiate even to this extent is of great value in the diagnosis of obscure cases.

The epinephrin hypersensitiveness test is regarded as mildly positive when, after the injection of 0.5 c.c. of 1 to 1000 epinephrin chlorid (adrenalin chlorid—Parke, Davis & Co.) solution a rise of about ten points in pulse or in systolic pressure or in both is obtained, and certain clear-cut subjective and objective signs and symptoms characteristic of

[1] In this chapter "hyperthyroidism" is used to include the Graves' syndrome. For discussion of the justification of such usage, see discussion of etiology of Graves' disease, p. 305.

hyperthyroidism are brought out. Normal subjects do not react to this dose (Peabody and others, Wearn and Sturgis) and therefore reactions from very mild to very marked must be considered respectively mild, moderate and marked positive responses. The exceptions stated by some as occurring in "effort syndrome" and even in so-called normal individuals, and in neurasthenics often do not give a typical, positive epinephrin response. The typical response is characteristically sustained and occurs in two phases, a primary major reaction followed by a secondary minor reaction. In one and one-half hours the reaction disappears, leaving the patient practically normal. Again, the response to the drug is parallel to the degree of toxicity clinically recognizable, in a way similar to the parallelism described for the metabolism determinations in the higher degrees of toxicity. After operation followed by subsidence of hyperthyroid symptoms there is a fairly prompt subsidence of the sympathetic hypersensitiveness to epinephrin.

The test is carried out as follows: The patient should preferably be put at rest in bed at least a day previously. If this is impossible, reclining for half an hour to an hour may be sufficient to obtain quiet and composure. The more composed the patient is at the time the test is carried out, the better, for under such conditions the reaction stands out more sharply by contrast. Having become acquainted with the attending physician who is to make the test, the patient is assured that the examination is in no way painful or dangerous. It cannot be emphasized too strongly that these precautions be observed in patients suffering with hyperthyroidism or similar conditions, for failure to do so has in many instances been responsible for the failure to obtain a sharp contrast reaction after the administration of the epinephrin. If one allows the patient to be disturbed by outside factors there is already a psychic reaction which, as is well known, is accompanied by increased pulse rate and blood pressure and by the exhibition of positive subjective and objective signs and symptoms which are characteristic of the epinephrin response. Under such conditions, it cannot be expected that a small dose of epinephrin should thereupon further increase the signs and symptoms as to be sharply positive. We must have a true norm on the part of the patient before the test is carried out.

Two or three readings of the blood pressure, systolic and diastolic, pulse rate and respiration are taken at five-minute intervals. These readings should be fairly constant. If they are not, time should be allowed for the patient to become calm. A note is then made in regard to the presence or absence of the subjective or objective status. This includes the subjective nervous manifestations, throbbing of the precordium, abdominal aorta or peripheral large arteries, heat and cold sensations, asthenia, and the objective signs, such as pallor or flushing of the hands

and face, increased size of the pupils, throbbing of the carotids and precordium, tremor, changes in temperature of the hands and feet, perspiration and any other characteristic signs or symptoms. The presence or absence of these signs is noted previous to the epinephrin injection for purposes of comparison with the manifestations following the injection. A hypodermic syringe armed with a fine needle which, when inserted, causes little discomfort is then used to inject deep subcutaneously 0.5 c.c. (7.5 minims) of the commercial 1-1000 solution of adrenalin chlorid (Parke, Davis & Co.) into the deltoid region.[2] The solution of epinephrin chlorid should be as fresh as possible. If the latter has been allowed to become dark-red or brown by action of the oxygen of the air it should be discarded, as this means that the drug has lost considerable of its potency due to oxidation. Failure to observe this precaution has been responsible for mistakes in the interpretation of the test. Readings of the pulse, blood pressure and respirations and any changes in the subjective and objective manifestations are then noted every two and a half minutes for ten minutes, then every five minutes up to one hour, and then every ten minutes for half an hour longer. At the end of one and one-half hours—sometimes earlier—the reaction has usually entirely passed off. The oft-repeated, early readings are made in order not to miss certain reactions on the part of the pulse and blood pressure that may come on in less than five minutes after the injection. Prompt responses are particularly prone to occur in cases of active hyperthyroidism.

In a positive reaction there is usually an early rise in systolic and a fall in diastolic blood pressures, in other words, a marked increase in pulse pressure. In a very mild reaction the fall in diastolic pressure alone may occur. In a definitely positive test the rise in blood pressure may be all the way from ten to as much as fifty or more millimeters of mercury. In the course of thirty to thirty-five minutes there is a moderate fall of the pulse and blood pressure, then the characteristic secondary slight rise and finally a second fall to the normal in about one and one-half hours. Together with these changes one sees an exaggeration of the clinical picture of Graves' disease or other forms of hyperthyroidism, especially the nervous manifestations. The symptoms of which the patient has complained are usually increased and often symptoms which are latent at the time of examination but which have previously been present are characteristically brought out. Thus, for example, in numerous instances there occur extrasystoles. The patients themselves are aware of these and recall having had them on previous occasions, doubtless, at times of clinical exacerbation of their disease. There

[2] A positive reaction is more convincing if the patient has given a negative response to an injection of isotonic salt solution administered under the same conditions as the epinephrin.—R. G. H.

are often increased tremor, apprehension, throbbing, asthenia, and in fact an increase of any of the symptoms of which the patient may have complained. There may be, furthermore, manifestations of symptoms latent previous to the injection and characteristic of the hyperthyroidism syndrome. Vasomotor changes are common and quite characteristic. Thus, an early pallor of the face, lips and fingers, due to vasoconstriction is common, and is followed in thirty minutes to an hour by the stage of vasodilation with consequent flushing, sweating and warmth of the face, hands and feet. The respirations at first become slower and deeper, even sighing in character, and later more shallow and rapid. Yawning is common. In fact, in a number of instances patients have fallen asleep during the test. They complain of considerable fatigue. The symptoms described have never been dangerous, and the manifestations produced by the test are no more than the disease itself produces and are transient, the status of the patient usually being quite normal in the course of an hour to an hour and a half.[3]

In order to interpret a test as positive it is necessary to have a majority of these signs and symptoms definitely brought out or increased. Thus, there is at times a considerable exacerbation of the objective signs and symptoms; there may be an increase of ten points in the pulse and blood pressure together with a moderate increase of symptoms and signs; there may be only slight changes in pulse and blood pressure and considerable change in signs and symptoms. Any combination of this kind may be regarded as positive. One must not regard a test as negative because there has not resulted from the epinephrin injection an increase or manifestation of all the possible signs and symptoms for, in order to gain a correct interpretation, one must consider the entire clinical picture produced, just as in the disease itself one cannot require every one of the characteristic signs and symptoms to be present in order to make a diagnosis.

In the exophthalmic goiter cases the epinephrin reaction in my experience has been uniformly positive and as a rule remarkably parallel in its manifestations with the severity of the symptoms. There is one qualification to the latter statement, however, and that is, that in the late advanced cases the reaction which one might expect to be very marked is only mild as a result of the fact that the nervous system, heart and other organs, having been severely damaged by the thyroid intoxication, are unable to respond to the epinephrin. The test in these cases is of course unnecessary for the diagnosis.

In the colloid goiter cases, without symptoms of hyperthyroidism,

[3] Very striking is the fact that patients giving marked objective evidence of distress, such as pallor, tremors and weeping, may deny any subjective discomfort whatever.—R. G. H.

the reaction is negative; in fact, in many instances of this kind a dose of 1 c.c. or larger is necessary to produce any symptoms resembling those seen in cases of hyperthyroidism. If, however, a colloid goiter is functionally overactive and then accompanied by symptoms of hyperthyroidism, the reaction is mildly or moderately positive.

In the adenoma cases, in which the adenoma or adenomata were found to be active by histologic examination and in which there were clinical symptoms of hyperthyroidism, the reaction was found to be positive and in proportion to the severity of the symptoms. In cases in which the adenomata had become degenerated and had lost their activity and were then naturally unassociated with clinical symptoms the reaction was nearly or entirely negative. In some cases in which there was a latent or quiescent period with absence of symptoms as a result of degeneration in an adenoma formerly active the symptoms could again be elicited by an injection of epinephrin. This was doubtless due to a certain degree of hypersensitiveness of the sympathetic nervous system which persisted for some time after the activity of the adenoma had disappeared.

In cases of adenomata of doubtful activity, operation is now being advised by the author, on the basis of a positive epinephrin test in the absence of which the diagnosis often remains entirely obscure. At operation adenomata too small to be seen or palpated on physical examination are often found and upon their removal striking benefits result. Accordingly, the test has led directly to a clearer conception of an obscure group of cases, which are dependent for their symptomatology upon a very definite pathological change in the thyroid gland. The author (*d*) (1920) has designated this condition "Diffuse Adenomatosis." The pathological condition is microscopic in character and recognized by a hyperplasia of the interstitial or "fetal" cells or tissue without accompanying hypertrophy or hyperplasia of the alveolar parenchyma. The symptomatology, much as in the adenoma cases, is a characteristic one, though, as a rule, unassociated with positive eye signs or microscopic changes in the gland. The symptoms are asthenia, nervousness, lability of the pulse but without definite constant tachycardia, emotional instability with mental symptoms, oftentimes loss of weight, vasomotor instability and a variable tremor. Without a positive epinephrin response and with a metabolic rate within normal limits, a point to be mentioned again, one would hardly feel that he was dealing with hyperthyroidism, and hence would hesitate to advise operation. By some, in fact, operation is felt to be contra-indicated because of the absence of increased metabolism. In such cases, however, the author has had striking success following thyroid resection.

In conditions of hypothyroidism, myxedema and cretinism, in which

there is increased tolerance to epinephrin, the injection test has served as a guide in the amount of thyroid gland administered, for it has been found that by using the standard dose of 0.5 cubic centimeter of epinephrin subcutaneously the gland therapy can with safety and benefit be increased to the point at which there appears a slight reaction. The amount of gland feeding indicated and at the same time compatible with safety can thus be determined as the proper dosage in a given case.

The epinephrin test has proved to be of the greatest value in the differential diagnosis of many conditions simulating hyperthyroidism, of which incipient tuberculosis is possibly the most important (Nicholson and Goetsch). It has been found, fortunately for the differentiation, that tuberculosis uncomplicated with hyperthyroidism gives a negative reaction to the test. This fact has afforded means for distinguishing early tuberculosis from hyperthyroidism, two conditions which clinically simulate each other so closely that mistakes in diagnosis are frequently made. Other conditions simulating hyperthyroidism and incipient tuberculosis, which might be mentioned, are psychasthenia, psychoneurosis, hysteria, neurasthenia, dementia præcox, melancholia, alcoholism, tabagism, acromegaly, arteriosclerosis, and several other diseases. Cases of this kind give essentially negative results with the test.

The importance of recognizing these conditions and separating from them the cases of true hyperthyroidism for which surgical relief can be offered need hardly be mentioned. In a few cases such as those mentioned some acceleration of the pulse and slight rise of blood pressure were observed but in all cases there was a complete absence of the subjective and objective symptoms so important in the interpretation of a positive test. Again, in these allied conditions there might be a slight transient reaction, whereas, in hyperthyroidism cases the reaction characteristically lasts from an hour to an hour and a half.

The test has been of value, furthermore, in estimating the degree of toxicity present in early exophthalmic goiter. A markedly positive reaction is often a better criterion than clinical judgment in helping to decide as to whether an exophthalmic goiter patient can safely undergo operation. The surgeon is thus warned in instances of this kind by a strikingly sharp preoperative epinephrin reaction, in which case the patient is advised to take a period of bed rest. If this has been done, a preliminary ligation of the thyroid arteries is performed. In cases in which there is a moderately sharp preoperative reaction, a thorough resection of the gland is indicated in order to gain a prompt improvement. If, in a year or more in the case of a single lobectomy in exophthalmic goiter, the symptoms have not improved to the desired degree and the epinephrin reaction is still definitely positive a second operation for removal of the remaining lobe is advised. After the second re-

section the epinephrin sensitiveness as a rule gradually disappears. In the case of subjects suspected of having possibly hyperthyroidism but in whom there is a negative epinephrin reaction operation is not advised, for it has been found that these individuals are rarely if ever benefited by operation.

In brief, the author does not hold that the epinephrin chlorid test is pathognomonic of hyperthyroid states. He would say, however, that a negative test excludes hyperthyroidism; that in all cases of hyperthyroidism the test is positive, that there are some few conditions which give a more or less typical reaction, and which are to be remembered as exceptions. The latter, he thinks, can be fairly well recognized after a careful history and physical examination. At any rate, he feels that the test is practically always confirmatory, in many cases diagnostic and in others suggestive of the diagnosis. It has led to further and more careful search for causes in the small percentage of exceptions. There is a remarkable parallelism between the hypersensitiveness to epinephrin and the degree of clinical hyperthyroidism present. The test has the distinct advantage of being easily made. From a therapeutic standpoint one can by means of the test follow the well known variations in the degree of hyperthyroidism present from time to time and regulate the amount of gland feeding accordingly.

Furthermore, the test has many advantages over either the metabolic rate determinations or the hyperglycemia test in that it is readily understood, performed and interpreted. It is not subject to errors of possible defective apparatus, requires no special training to carry out, is inexpensive, involves no calculations and is accompanied by a minimum of inconvenience and annoyance to the patient. In the mild and latent cases of hyperthyroidism it seems to be more sensitive and therefore more diagnostic than the metabolic rate tests. It is not subject to the great variations found in the case of the metabolic determinations under different circumstances and in the hands of various observers. It would seem that in one important group, at any rate, namely in the obscure adenoma and adenomatosis group of thyroid disorders (Woodbury), a positive epinephrin test reveals the diagnosis whereas the metabolic rate determination, being within normal limits, fails to indicate the presence of a latent hyperthyroidism. The author has also seen cases of this kind. On the other hand, in cases of hyperthyroidism of severer grades of toxicity the epinephrin determinations run as a rule remarkably parallel to the curve of increased metabolism (Woodbury). It is possible that in the mild and latent hyperthyroidism of adenoma and diffuse adenomatosis we are dealing with an altered secretion, which has a stimulating effect upon the sympathetic nervous system and is therefore discoverable by a positive epinephrin test, whereas, failing to produce an increased metabolism, it might escape recognition.

Basal Metabolism Determinations in Thyroid Disorders

Principles of Basal Metabolism.—To Friedrich von Müller (*a*) and Magnus-Levy (*a*) belongs the credit of first (1893-1895) pointing out that one of the most characteristic phenomena of hyperthyroidism is an increase in general metabolism, while in hypothyroidism there is a diminished metabolism. They suggested, further, that these peculiarities depend on the regulatory action of the thyroid secretion on metabolic processes. It would seem, therefore, that the optimum conditions of body function are dependent on a definite quantity of thyroid and synergistic secretions which can vary only within narrow limits without producing more or less serious disturbances. They noted further that in Basedow's disease patients tended to become emaciated and that the metabolism was of a labile character expressing itself characteristically in alternating periods of emaciation and of increase in weight although a good appetite was usually present.

Magnus-Levy (*a*) (1895) was the first to make a systematic study of the respiratory exchange in Basedow's disease and pointed out that along with the emaciation, tachycardia and elevation of temperature, the respiratory exchange and heat production per kilogram and minute showed values far in excess of those of healthy persons of the same size and weight. He further reports two cases of recoveries from Basedow's disease, in which the subjects showed normal respiratory rates. In some instances of severe hyperthyroidism the respiratory exchange reaches a point as much as 100 per cent above the normal. Between this point and the normal there are all possible variations of respiratory rates depending upon the severity of the thyroid intoxication (Du Bois, 1916; Sandiford, 1920).

In this country Du Bois was unquestionably the pioneer in the study of metabolism in hyperthyroidism. His results and a review of the German literature are given in his paper published in 1916. Du Bois was the first to study metabolism in exophthalmic goiter by means of a respiration apparatus, which was also a calorimeter. He believed that measurement of the heat production gave the best index of the severity of the disease and of the effect of treatment. Very severe cases showed an increase of 75 per cent or more above the normal average, severe cases 50 per cent or more, and moderately severe and mild cases less than 50 per cent, while a few mild and several atypical and postoperative cases were found to be within normal limits.

Very soon after the discoveries of von Müller and Magnus-Levy attempts were made to measure the heat production and basal metabolism of subjects under various conditions and with various diseases. By the term "basal metabolism," or better, "basal metabolic rate," of an organism

is meant the minimal heat production of that organism, measured from twelve to eighteen hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined by direct calorimetry, that is by actual measurement by means of a calorimeter, or by indirect calorimetry, that is by calculating the heat production from an analysis of the end products which result from oxidation within the organism; in other words, from the amount of oxygen used and the corresponding amount of carbon dioxid produced, together with the total nitrogen eliminated in the urine, although for clinical work the urinary nitrogen may be neglected (Sandiford).

The experimental work of Lavoisier marks the beginning of researches on metabolism, and to him belongs the credit of pointing out that the life processes are those of oxidation with the elimination of heat.

In 1894 Rubner (*b*) constructed the first successful respiration calorimeter designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it and the simultaneous measurement of the quantity of heat produced by that organism. By means of this apparatus Rubner (*b*) verified the method of Pettenkoffer and Voit of calculating the heat production (indirect calorimetry) and proved that the law of conservation of energy holds for the living organism.

It was not until 1905 that the respiration calorimeter was brought to a high degree of technical perfection by Atwater and Benedict. With their apparatus it was possible to determine simultaneously with the measurement of the heat elimination, not only the carbon dioxid production, but also the oxygen consumption of the subject. They also confirmed the agreement between direct and indirect calorimetry. Lusk, Du Bois, Peabody, and their coworkers have likewise demonstrated, in a large series of pathologic conditions, the close agreement between the two methods. As a result of these investigations the use of such a complicated apparatus as the respiration calorimeter has been shown to be unnecessary for clinical work and in its place the comparatively simple method of indirect calorimetry to be adequate.

Carpenter has shown that for indirect determination two types of apparatus are suitable, the closed circuit and the gasometer. According to Sandiford, by far the best apparatus of the closed circuit type is the Benedict (*a*) unit apparatus. By means of a mask, mouthpiece or nasal tubes, the subject rebreathes air from a closed system in which the carbon dioxid is absorbed by soda lime, and, as the oxygen is used up, it is replaced by oxygen in known amounts. The air within the apparatus is kept in constant circulation by means of a blower. A small spirometer is inserted in the circuit as an expansion chamber and volumetrically records the respiratory movements on a smoked drum. Knowing the weights of oxygen used and the carbon dioxid eliminated, one can readily

calculate the heat production. This unit apparatus has, however, some disadvantages for clinical work. It is rather cumbersome. Constant checking is required to see that it is absolutely air tight, for a leak of 20 to 30 c.c. during a fifteen-minute determination will appreciably affect the results, because such a leak in this type of apparatus will be equivalent to the loss of so much oxygen and not equivalent to the loss of so much air as is the case in the gasometer method. Furthermore, the accumulation errors of the apparatus fall on the oxygen and not on the carbon dioxid determination, thus causing an error in the calculation of the respiratory quotient and heat production. The absorbing chemicals must be changed frequently and with the repairing and constant checking of the apparatus it is on the whole difficult to use in clinical work.

The portable respiration apparatus [4] recently devised by Benedict (*b*) for clinical work is a modification of his unit apparatus described above. It is designed primarily to give a rapid and at the same time a comparatively accurate measurement of the oxygen consumption without involving analysis or weighing. The difficulties inherent in the closed circuit type of apparatus are still present in the portable apparatus. Sandiford at the Mayo Clinic has not adopted this method, as she prefers to determine not only the oxygen consumption, but also the carbon dioxid elimination since the heat production can thereby be more accurately calculated.

For clinical work Sandiford used the gasometer method introduced by Tissot in 1904 and considers it the most satisfactory. "Briefly, the determinations are made in the following manner: A mask is adjusted over the patient's mouth and nose and by means of expiratory and inspiratory valves the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of carbon dioxid and oxygen content of the expired air, the analysis being done in the Haldane gas analysis apparatus. Since the ventilation rate for each minute is known, as well as the amount of carbon dioxid produced and the oxygen absorbed, it is possible to calculate by means of calorie tables the total number of calories produced each hour." The method of routine determinations of the basal metabolic rate is then more fully discussed, to which reference should be made (Sandiford, 1920, p. 74).[5]

One of the chief advantages of the gasometer method is that, should a leak of a few cubic centimeters occur around the mask the end result is not appreciably affected, while a leak of a similar volume in the closed circuit

[4] The Benedict portable respiration apparatus is manufactured and sold by the Sanborn Company, 79 Sudbury Street, Boston, Mass.

[5] The details of the technic are described in a laboratory manual by Boothby and Sandiford. The apparatus may be obtained from H. N. Elmer, 1136 Monadnock Bldg., Chicago.

apparatus has a value at least five times as great, because in the latter case it is equivalent to the loss or gain of so much pure oxygen.

The calculation of the basal metabolic rate is very simple. Knowing the volume of air expired by the patient in a minute (the ventilation rate) and the percentage of carbon dioxid and oxygen in the expired air, it is possible to calculate the volume of oxygen absorbed by the patient in one hour, as well as the corresponding amount of carbon dioxid produced. Since the respiratory quotient, that is the ratio between the volume of carbon dioxid produced and the volume of oxygen absorbed, indicates the kind of food being burned at the time of the determination, and since by means of calorie tables the calorific value of one liter of oxygen absorbed by the body in the burning of these substances is known, the total heat production each hour can be readily calculated. The total number of calories must be divided by the surface area, a factor correlated with the patient's height and weight. The number of calories for each square meter of body surface each hour must then be compared with the normal standards of comparison which are dependent on the age and sex of the patient. For convenience, basal metabolic rates are expressed in percentages of the normal, and when the heat production is greater than the normal the percentage is plus, and when less than normal the percentage is minus. (Sandiford).

Some difficulty has been experienced in making satisfactory determinations of the area of body surface and hence of the heat production. Rubner (*a*) suggested that the heat production of an individual is proportional to his surface area. For the determination of the surface area Meeh proposed the formula: Surface area in square centimeters = 12.3 (a constant) × weight in grams $^{2/3}$. There were, however, some errors in calculations based upon this formula, due in greater part to the fact that the height of the subject was neglected. As a result of further studies Du Bois and Du Bois (*a*) (*b*) devised a formula based on height and weight by means of which the surface area can be calculated with an average error of 1.7 per cent. This formula is:

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

where A is the surface area in square centimeters, W is the weight in kilograms, H is the height in centimeters and 71.84 is a constant. On the basis of this formula they then constructed a height-weight chart by means of which the surface area can be estimated at a glance. Du Bois, using this new height-weight chart for the determination of the surface area in conjunction with his standards of normal basal metabolism with regard to age and sex, further showed that the metabolism of normal persons can be predicted with an accuracy of ± 10 per cent. This fact has been confirmed both by Means (*a*) and by Boothby.

Benedict has criticized the method of predicting the heat production from the unit of surface area. In practical clinical work, however, the determinations of the basal metabolic rate, using the standard of Du Bois, have been found satisfactory.

The method of direct and indirect calorimetry were found to agree very closely when one considers the technical difficulties. The method of direct calorimetry gave results which were slightly lower than the indirect, the total difference being 2.9 per cent. This and the absence of abnormal respiratory quotients show that the law of conservation of energy holds good in exophthalmic goiter, and that there is no profound disturbance of the intermediary metabolism.

One small cretin 36 years old produced about half the calories eliminated by children of his size. As estimated by the surface area, his metabolism was about 20 per cent below the normal adult level. Three and a half days of treatment with thyroid extract raised his heat production to normal.

Means and Aub (*a*) (*b*) (*c*) have made an extensive study of exophthalmic goiter from the point of view of the basal metabolism. A preliminary outline of their work was made in 1917, to be followed in 1919 by two papers, the first giving their results in a study of basal metabolism in hypothyroidism, and the second giving their final results in a study of exophthalmic goiter. They used the level of heat production as an index of the effect of medical treatment.

Since the metabolism in hyperthyroidism was found to be considerably above normal, then one should find in cured cases of Basedow's disease rates approaching the normal. This was found by Magnus-Levy to be true in two cases observed as early as 1895 and has been abundantly confirmed since. When the metabolic rate is high the risk of operation is considerably greater and preliminary treatment with Röntgen-rays was therefore recommended by Means and Aub (*c*). Similarly, other measures for preliminary reduction of thyroid activity and of the metabolic rate, therefore, have been used, particularly ligation of the thyroid arteries. Although in three out of four cases Du Bois found an increase in metabolism, this has not been the rule. On the contrary, one generally finds an improvement in the clinical condition and a fall in the metabolic rate (Sandiford, 1920). After thyroidectomy, usually though not always, a gradual fall of the metabolic rate coincident with the clinical improvement is observed. Means and Aub (*c*) used the metabolic rate as an index to the improvement after various forms of therapy, and stated that the results after Röntgen-ray treatment after two to three years were as good as with surgery and recommended this treatment as a preoperative measure.

Hypothyroidism shows a decreased metabolism (Magnus-Levy (*a*), 1895). Du Bois found, as stated above, in a small cretin 36 years old that

the metabolism was about 20 per cent below the normal adult level. It is interesting also that he was able to raise the heat production to normal in three and a half days' treatment with thyroid extract. Means and Aub (*b*) found that in myxedema there is also a diminished basal metabolism. They found that three cases of untreated myxedema showed a definite reduction below that of normal individuals of the same age and sex. In the treatment of hypothyroidism, doses of from three to four grains of thyroid extract daily should be ample to bring the metabolism to normal in two or three weeks, and doses of from one to two grains daily should usually be sufficient to keep it there. Similarly, the basal metabolism in an untreated cretin and in a case of cachexia strumipriva showed a marked reduction (Sandiford). Du Bois (1916) found that treatment with thyroid extract raised the heat production and metabolism, while Means and Aub (*b*) found that the metabolism of all the patients studied during thyroid therapy was readily brought to normal or above, by the administration of thyroid extract. They also regarded the basal metabolism as an index to the effect of treatment and believed, furthermore, that it furnished a far better guide in this respect than does the clinical picture. They found also that cases of cachexia strumipriva need larger maintenance doses than do those of spontaneous hypothyroidism. Finally they believe that in the management of exophthalmic goiter periodic determinations of the basal metabolism should be quite as much a routine as is the examination of the urine for sugar in diabetes mellitus. Furthermore, in borderline cases the basal metabolism furnishes very valuable aid in the differential diagnosis.

As Boothby has stated: "No factors other than the 'autacoids' have yet been discovered which are known to influence basal metabolism, with the possible exception of the toxins of fevers. Therefore, it seems logical to reverse the accepted theory and, except in the case of infections, to suggest the tentative hypothesis that a variation of the basal metabolism beyond normal limits is due to an abnormality in the secretion of one or more of the endocrin organs. The particular autacoid must then be sought for by characteristic localizing symptoms and by the elimination of those autacoids variations of which produce well-known signs and symptoms."

Uses of Metabolic Rate Test

The metabolic rate test can be used with distinct advantage in the study of thyroid disorders, for example, in the early diagnosis of hyperthyroidism, in which case an early increase in the metabolic rate together with other clinical signs and symptoms would be very suggestive indeed. The measurement of the heat production gives a very accurate index of the severity of the case and of the degree of hyperthyroidism

in a given patient at a given time (Cistrunk, Du Bois, Sandiford). The metabolic rate parallels closely the clinical picture presented by the patient and also the pulse and pulse pressure. The level of the heat production is used as an index of the effectiveness of the medical treatment (Du Bois). The metabolic rate has afforded great help in determining the proper method of treatment in conditions of over- or under-activity of the thyroid and, when taken before, during and after treatment, has shown the value of that treatment, whether beneficial or harmful. Similarly, the basal metabolism forms a guide for governing this dosage in cases of hypothyroidism (Means and Aub (*b*)). Again, it has been of great help in the differential diagnosis in obscure cases such as the neuroses, neurasthenia and chronic nervous exhaustion which may simulate hyperthyroidism but in which there is no definite increase of the metabolic rate. Again, a high metabolic rate is often a warning against surgical measures (Cistrunk) and in those cases in which the metabolic rate is found to be rising, complete rest in bed is indicated together with preliminary ligations of the thyroid arteries or treatment with the Röntgen-rays. Again, the metabolic rate when frequently determined enables one to follow the management of the exophthalmic case. The surgeon is also helped, for he is enabled to choose more intelligently the type of operation indicated in a given case. He is also able to decide better as to the amount of tissue to be removed and as to when, in a case in which a complete cure is not obtained, second operation should be done.

There are certain disadvantages due to technique and interpretation in the application of the basal metabolism test in the diagnosis of hyperthyroidism. Thus, unless the greatest care is taken to prevent all muscular activity, an increase in basal metabolism always results. A substantial error would be introduced if one failed to measure exactly the duration of the observation or allowed escape of air or oxygen around the mouthpiece, or if proper care were not taken to correct the volume of oxygen to zero C. and sea-level barometric pressure. Again, there are some difficulties of interpretation of the metabolic determinations, for there are some striking exceptions to what would be warranted suppositions with regard to an individual case. Thus, occasionally a case clearly active clinically fails to show any striking increase in metabolism, and vice versa (Sandiford, Cistrunk). Furthermore, basal metabolism has been found increased in some conditions other than hyperthyroidism, as in certain types of endocrin disorders, fever and acidosis. Thus, for example, Means (*b*) (1915) found an increase in an undoubted case of hypopituitarism showing obesity and a high sugar tolerance. He also found increased metabolism in starvation acidosis as has been found by others in the acidoses of diabetes and in normal subjects on a carbohydrate-free diet. Tompkins and Brittingham (1919)

have described increased metabolism in some cases of pernicious anemia. These exceptions are difficult to explain.

The Hyperglycemia Test

Relation of the Thyroid to Carbohydrate Metabolism.—Thyroid secretion plays a very important rôle in the carbohydrate metabolism of the body. Thus, it has been shown by King that the thyroid gland exerts a retarding action on the carbohydrate-destroying mechanism of the body as does also the active constituent of the gland, "iodothyrin," even in a more marked way. This action of the thyroid is quite independent of any relationship with other endocrin glands or with the nervous system. It would seem that the thyroid inhibits the direct combustion of sugar in the muscles, probably by inhibiting the action of the pancreatic and muscle ferments which cause the actual oxidation of dextrose. Furthermore, it has been shown by Kuriyama that thyroid feeding to white rats produces a decreased glycogen content of the liver. He did not find, however, that experimental hyperthyroidism produces any change in the sugar content of the blood in either rats or rabbits.

Other hypotheses have been advanced to explain the production of hyperglycemia in hyperthyroidism. Some believe that the thyroid secretion acts on the suprarenal glands stimulating them to increased activity, or that the thyroid hormone acts on some other of the endocrin glands concerned in sugar metabolism. Allen believes that the hyperglycemia is produced by the action of the thyroid on the nervous system. It is as a result of these influences, doubtless, that increased amounts of blood sugar have been found in hyperthyroidism and in extreme cases occasional glycosuria. The determination of this increased sugar content of the blood has led to the confirmatory hyperglycemia test.

Carbohydrate Tolerance in Experimental and Clinical Hyperthyroidism

The sugar content of the blood does not change in experimental hyperthyroidism (Kuriyama) nor does spontaneous glycosuria result from thyroid feeding in either rats or rabbits. The tolerance for dextrose parenterally administered to thyroid-fed rabbits does not differ from that of normal animals (Kuriyama). Turning now to clinical hyperthyroidism, we find that spontaneous glycosuria has long been known to occur in exophthalmic goiter (Kraus and Ludwig, Chvostek, von Noorden (*b*), Garrod (*a*)). This is doubtless due to the fact that the normal use of carbohydrates is made more difficult by the increased amounts of thyroid

secretion, a fact which has been shown to be true experimentally as well. It has been shown further, that in Basedow's disease, with or without spontaneous glycosuria, there is a lowered assimilation limit for carbohydrates (Kraus and Ludwig, Straus, Geyelin, O'Day (*a*)). Alimentary glycosuria was demonstrated by Goldschmidt in exophthalmic goiter and was shown to occur also after thyroid administration. Wilder and Sansum found that the intravenous glucose tolerance in health was approximately 0.8 gm. per kilogram of body weight per hour. No glycosuria occurred with this dose but when 0.9 gm. were injected per kilogram per hour sugar appeared in the urine. When comparing this normal tolerance with the intravenous tolerance in five cases of exophthalmic goiter they found that in all of the latter there was a reduction in tolerance varying from 0.5 gm. to 0.7 gm. per kilogram per hour according to the severity of the cases, the more severe showing the lower degrees of tolerance.

Carbohydrate Tolerance in Hypothyroidism.—The converse of these findings should occur whenever there is produced in an organism, either experimentally or clinically, a diminution in the amount of thyroid secretion. For example, it has been shown that after removal of the thyroid gland there is a rise in the assimilation limit for dextrose (McCurdy). A great many observations have been made in recent years to show that in myxedema there is an increased sugar tolerance. Thus, for example, Hirschl found that in an outspoken case of myxedema the administration of from 200 to 500 grams of grape sugar did not produce alimentary glycosuria. Other observers have noted (von Noorden (*b*)) that whereas spontaneous glycosuria is not uncommon in exophthalmic goiter, it is so rare as practically never to occur in myxedema.

Blood Sugar in Hyperthyroidism.—The occurrence of alimentary hyperglycemia in hyperthyroidism has been known since the work of Tachau (1911) and Garrod (*a*) (1912). At that time, however, there was a lack of uniformity in the methods of estimating blood sugar, and these were at the same time too cumbersome for ordinary clinical use. It is only in recent years that methods of determining blood sugar have been sufficiently simplified and controlled to be of real clinical use. The labors of Lewis and Benedict (1915) have placed this work on an entirely different, clinically practical basis. They introduced a very simple and accurate colorimetric method depending upon precipitation with picric acid. Their method for the determination of sugar in the blood depends upon a color obtained by heating a dextrose solution with picric acid and sodium carbonate. In the case of the blood, protein is removed by precipitation with picric acid. This is then treated with picric acid and sodium carbonate and evaporated. The residue is redissolved and the color compared with the standard glucose-picric acid-sodium carbonate solution or the picramic acid standard. It was found that in normal persons the average sugar content of the blood equals 0.10 per cent and this

agrees with the results of others. Hyperglycemia is considered to be present when the blood sugar content rises above 0.10 per cent. Myers and Bailey simplified the method of Lewis and Benedict. An initial blood dilution of 1 to 5 instead of 1 to 12.5 is used and in this way a sufficiently low concentration is obtained to obviate the necessity for evaporation in the development of the color. For this determination the Hellige colorimeter has been found especially satisfactory. In all other essential respects the method is that of Lewis and Benedict. By the use of these colorimetric methods the determination of blood sugar has been placed upon a practical clinical basis, and as a result it has now been abundantly shown that in hyperthyroidism there is a diminished tolerance of carbohydrates with alimentary hyperglycemia followed by glycosuria whenever the hyperglycemia exceeds the renal glucose threshold of the individual case (McCaskey). In every case of hyperthyroidism which McCaskey studied, after the ingestion of 100 gms. of glucose the blood sugar content was increased within two hours from 50 to 200 per cent. In 70 per cent of 31 cases the maximal rise occurred at the end of the first hour with a more or less sharp decline at the end of the second hour, proving that the crest had been reached and passed. The very few cases in which hyperglycemia is highest at the second hour he thinks are explained by gastric hypomotility and slow intestinal absorption.

Denis, Aub and Minot carried out a series of experiments dealing with the effect produced by carbohydrate ingestion upon persons suffering from hyperthyroidism. Coincident with these experiments they made observations on the gaseous metabolism of these patients with the idea of establishing if possible some relation between the increase in metabolism found in this condition and the effects produced on the blood sugar level by the ingestion of carbohydrate. The blood sugar determinations were made by the method of Lewis and Benedict as simplified by Myers and Bailey, 2.4 c.c. of blood being used for each determination. Qualitative and quantitative determinations of sugar in urine were made by Benedict's methods. More recently another method, also colorimetric, for the determination of sugar in small quantities of blood has been devised by Folin. By some this method is felt to be simpler and to afford less chance for error than the Myers and Bailey method.

Method of Procedure.—Between 7 and 8 A.M. the patient who has received no food since 5 o'clock on the previous afternoon is given 100 gms. of glucose, 50 gms. of bread and 20 gms. of butter. Just previous to this meal a sample of urine is secured and five cubic centimeters of blood are taken by venepuncture. Samples of blood and urine are then obtained at hourly intervals, from three to five samples of blood being taken from each patient. The method used for determination of the metabolism is that described by Benedict (1918 (*b*)).

Results in a Number of Normal Subjects.—They found that in normal subjects the fasting blood sugar shows a minimum value of 0.09, a maximum of 0.12 and an average value of 0.10 per cent. In most normal persons the ingestion of 100 gms. of glucose and 50 gms. of bread causes no increase in blood sugar two hours or even one hour after breakfast. Fasting hyperglycemia is of rare occurrence in hyperthyroidism, whereas alimentary hyperglycemia lasting in some cases for four hours after the ingestion of carbohydrate is invariably present.

Summary.—Fasting hyperglycemia is of extremely rare occurrence in hyperthyroidism. Alimentary hyperglycemia following the administration of 100 gms. of glucose and 50 gms. of bread was observed in every case examined. No relation could be found between the degree of hyperglycemia and the intensity of glycosuria. Neither was it possible to obtain any evidence of a relation between the severity of intoxication, as measured by the percentage increase over normal of the basal metabolism, and the occurrence of hyperglycemia. In a number of cases it was found, however, that after improvement of the patient's condition by resting or by operation the alimentary hyperglycemia was of a much lower grade than that induced by the same test given before treatment. In two cases of hypothyroidism no change was noted in the fasting blood sugar after the administration of thyroid extract.

Clinical Value of the Hyperglycemia Test.—Although alimentary hyperglycemia is commonly found in hyperthyroidism, it is in no sense specific for this disease, nor is it proportional to the degree of thyrotoxicosis since it is influenced by many other factors. Hyperglycemia is, of course, known to occur in diabetes, in nephritis in which it may reach 0.2 per cent (Myers and Bailey) and also in edema. It was shown by Hamman and Hirschman that alimentary hyperglycemia may occur even in normal cases, the blood sugar rising to 0.15 per cent. A certain number of otherwise normal cases have a low renal threshold for glucose so that sugar appears in the urine although the blood remains below 0.14 per cent. They also showed that the blood sugar curve, in hyperthyroid patients, after the ingestion of 100 gms. of glucose has to some extent the high, sustained and prolonged features of the diabetic type, whereas in normal persons under similar conditions there is only a moderate hyperglycemia that rapidly subsides, the blood sugar remaining below 0.15 per cent and again reaching the fasting level, or in many instances a still lower level, in from one to two hours. Hyperglycemia has been noticed also in cases of edema and in certain cases of arthritis.

In view of the facts, then, that alimentary hyperglycemia and even spontaneous glycosuria is fairly common in hyperthyroidism; that hyperglycemia is found also in a number of other diseases and pathological conditions; that the degree of hyperglycemia is not parallel to the degree of thyrotoxicosis; that these carbohydrate changes are not specific for

thyroid disturbances, and that the hyperglycemia is influenced by so many other factors, such as nephritis, it is impossible for us to interpret the hyperglycemia test as pathognomonic of hyperthyroidism. The finding of glycosuria and hyperglycemia in other pathologic conditions, such as fever, alcoholism, neurasthenia, and in the various endocrinopathies somewhat nullifies its significance; but if these can be excluded, its presence is highly suggestive. When rationally corroborated with the remaining clinical data this test is confirmatory.

Further reliance must be placed upon the basal metabolism and epinephrin hypersensitiveness tests.

The Specific Ferment Test of Abderhalden in the Diagnosis of Hyperthyroidism

Lampé and his coworkers have made extensive studies upon the possibility of applying the Abderhalden test to the diagnosis of thyroid disorders. They believe that the blood serum of patients suffering with hyperthyroidism contains ferments which are specific for thyroid tissue and for exophthalmic goiter gland. They feel that, if in cases of hyperthyroidism there is an overproduction of normal thyroid secretion, a negative result with the Abderhalden test should be obtained, for in such a case there is introduced into the blood merely an increased amount of a purely native protein. There is, therefore, no production of ferments. If, on the other hand, there is present in the blood a protein secreted by the thyroid but of an altered composition on account of the pathological changes in the gland, then this foreign protein would stimulate the production of a specific ferment and the Abderhalden reaction would be positive. They studied the digestive ferment action of the serum from cases of Basedow's disease upon normal, exophthalmic, cystic and parenchymatous thyroid gland, upon normal and hyperthyroidism thymus, and upon ovary, testicle, kidney, suprarenal and pancreas. In all cases in which the serum from cases of hyperthyroidism was allowed to act upon thyroid gland from hyperthyroidism cases, the gland was digested. In relatively few cases was the reaction positive when normal thyroid tissue was used. The reaction was positive also in four of the five cases of cystic goiter and in the cases in which thymus and ovary were used. With other tissues the reaction was negative.

In the serum of myxedematous patients there is similarly an antiferment for thyroid tissue, a fact which seems to indicate an abnormal thyroid activity, though the functional disturbances of the thyroid in myxedema are evidently of a very different character than in Basedow's disease. In other words, Lampé feels that the secretory dis-

turbance in exophthalmic goiter is one affecting more the character of the secretion than its amount. He believes further that in cases of "hyperthyroidism" there is a true dysthyroidism with the production of a secretion differing from the normal. This view is supported by the fact that the serum of the patients with exophthalmic goiter digested exophthalmic goiter tissues, but not the normal gland except in very few instances.

Two distinct methods have been devised for detecting the presence of the antibodies upon which the Abderhalden test is based, the first the optic method, and the second the dialyzation method. The first requires considerable skill and technical ability as well as rather expensive apparatus. The second, the dialyzation method is much simpler both in technic and necessary equipment. Both of these methods require the most assiduous attention to the various details given, if any reliance is to be placed on the results. Thus far the Abderhalden ferment test has not proved to be of practical clinical value.

The Aceto-Nitrile Test of Reid Hunt for Hyperthyroidism

Reid Hunt found in a small series of determinations that mice when fed upon thyroid gland developed an increased tolerance for aceto-nitrile or methyl cyanid (CH_3CN). He found that this reaction was specific for thyroid tissue and more delicate than any chemical test. He furthermore suggested that the increased resistance to aceto-nitrile might be used as a delicate test for thyroid substance and also as a means to determine whether there is an increased amount of thyroid secretion in the blood in cases of hyperthyroidism.

The test is carried out by giving mice 1 or 2 c.c. of blood taken from a suspected case of hyperthyroidism. The blood is mixed with meal and given for nine or ten days before the mice are tested for their resistance to aceto-nitrile. A series of control animals is used. In recording results it is borne in mind that one-fourth of a milligram of aceto-nitrile per gram of body weight of mouse may be fatal to a normal animal in a few hours.

Hunt's experimental series was too small to enable one to draw final conclusions and although the results have been partially confirmed the exceptions and qualifying results of others have been so many as to render the test of interest but of no real clinical value. Thus Ghedini found that the injection of 20 milligrams of dried thyroid extract in eleven days time is sufficient to raise the resistance of the animals to withstand twenty times the fatal doses of aceto-nitrile. Hunt's results have been partially confirmed by Trendelenburg. The latter, however,

does not believe that the resistance to aceto-nitrile is in proportion to the percentage of iodin in the thyroid tissue as was maintained by Hunt. Ghedini concludes that the reaction of thyroid extract in increasing aceto-nitrile resistance is specific. His finding that the iodin content is without appreciable effect upon resistance confirms Trendelenburg's findings but refutes those of Reid Hunt. In brief, the aceto-nitrile has not proved to be of real clinical value.

Two other tests might be briefly mentioned. They are of considerable interest but of little diagnostic value. They are the test of Claude, Baudouin and Porak, and the Marinesco-Roseo complement deviation test for hyperthyroidism.

The Test of Claude, Baudouin and Porak for Hyperthyroidism

This test is characterized by the production of bradycardia by the subcutaneous injection of pituitary posterior lobe solution in cases of hyperthyroidism. In normal cases, under these conditions there is an acceleration of the pulse. The former inhibitory effect upon the pulse rate is thought to be due to stimulation of the vagus nerve, whereas in cases without hyperthyroidism a stimulating effect is produced upon the sympathetic accelerator nerves to the heart. These authors feel that in cases of hyperthyroidism there exists a tachycardia which is due to hyperexcitation of the sympathetic nervous system as a result of which the sympathetic does not react to the pituitary extract. On the other hand, the nerve endings of the vagus which are not excited feel the full effect of the pituitary stimulation and the pulse rate is retarded. This test does not take into account the many cases of latent hyperthyroidism, particularly those dependent upon adenoma or diffuse adenomatosis in which there is no preëxisting tachycardia, and in which the results of the test would therefore be negative entirely or nearly so, the pulse in these instances often being normal or even subnormal.

Marinesco-Roseo Complement Deviation Test

These authors suggested that in states of hyperthyroidism there is sufficient thyroid substance (antigen) present in the blood serum to give rise to the formation of antibodies in the patient's blood. They proposed to test for these antibodies by means of antigen prepared from thyroid gland removed at operation from cases of hyperthyroidism. The experimental and clinical results are not sufficient or conclusive enough to warrant more than mention of this test and, therefore, opinion is withheld as to its clinical diagnostic value in states of hyperthyroidism.

Therapeutic Test with Iodine and Thyroid Extract

It is a well known fact that the administration of iodids over long periods to cases of goiter may produce symptoms of hyperthyroidism (Kocher). Fr. von Mueller suggested the use of iodin in small amounts for the purpose of disclosing hyperthyroidism, for in those suffering from the latter there is often an intolerance to iodin which produces emaciation and tachycardia after its administration. Thyroid extract has also been used as a therapeutic test to disclose a latent or incipient hyperthyroidism. Graded doses of thyroid extract are taken at four-hour intervals daily for three or four days or less if the characteristic symptoms of hyperthyroidism are produced earlier. The pulse rate is taken in the morning, afternoon and evening before thyroid feeding is begun and daily thereafter until symptoms are produced. After the administration of small amounts of thyroid extract in cases of hyperthyroidism symptoms and signs are brought out, such as irritability, twitchings, dyspnea, nervous manifestations, increased pulse rate, perspiration and tremor, these symptoms being produced earlier and on smaller doses of thyroid extract than in normal individuals or, more particularly, in those with hypothyroidism.

In the latter instance relatively large doses can be given over a considerable period without producing symptoms of hyperthyroidism. In cases of hyperthyroidism the pulse rate often does not return to normal even after the cessation of thyroid administration. In fact, it may continue to be rapid and irregular for several days.

There is an element of danger in the administration of iodids, iodin or thyroid gland extract to show a latent hyperthyroidism. The duration of the test is too long, it requires the patient to be in bed for two, three or more days; it is associated with a considerable period of discomfort, and in the end the results are not clear-cut and precise and, therefore, not particularly diagnostic. These tests cannot be applied in a routine clinical way.

Epinephrin Mydriasis Test of Loewi

Loewi found that in pancreatectomized animals, in human diabetics and in cases of hyperthyroidism the instillation of a few drops of 1 to 1000 solution of epinephrin produced dilatation of the pupils. He believed that the internal secretions of the thyroid and suprarenal glands are synergistic and that both act by stimulating the sympathetic nervous system. In cases of hyperthyroidism the sympathetic nerves should therefore be in a state of irritability. As a result the dilator fibers of the

iris, governed by the sympathetic, respond abnormally to the action of epinephrin.

It is true that this mydriasis test of Loewi is positive in the higher degrees of hyperthyroidism, but the results are somewhat uncertain when the test is applied to cases of latent or incipient hyperthyroidism. It is, of course, in these cases that a test should be of the greatest use. Loewi's test is of considerable interest, nevertheless, and confirmatory in the higher degrees of hyperthyroidism which are, however, recognizable without it.

SECTION III

The Parathyroid Glands and Their Diseases

Anatomy, Embryology, Comparative Anatomy and Histology of the Parathyroids ..... *E. V. Cowdry*

Anatomy—Gross Morphology and Relations—Blood Supply—Lymphatics—Innervation—Embryology—Origin—Growth—Comparative Anatomy—Histology—Histologic Morphology—Cytology—Functional Relation to Thyroid—Variations. (From the Anatomical Laboratory, Peking Union Medical College.)

Anatomy, Embryology, Comparative Anatomy and Histology of the Parathyroids

E. V. COWDRY

NEW YORK

Anatomy

Gross Morphology and Relations.—The parathyroid glands are small bean shaped structures about six millimeters long, three millimeters broad, and two millimeters thick, weighing in all about fifty-five centigrams, but so great is the variation that no two investigators ever give the same figures. Their number is variable, ranging from four to five or six, or as many as eight. Usually they are found in two pairs, superior and inferior.

The superior parathyroids are thought to be rather more constant in position. They occur on the medial aspect of the dorsal surface of each lateral lobe of the thyroid gland, at about the junction of its upper and middle thirds (Fig. 1). Sometimes they are embedded in the substance of the gland in lower forms, but in man they are usually separated from it by the thyroid capsule. Nevertheless, they are often called "internal," as contrasted with the inferior or "external" glands.

Fig. 1. Dorsal view of thyroid and parathyroid glands from Lewis, after Halsted and Evans.

The inferior parathyroid glands likewise occur on the dorsal surface of each lateral lobe of the thyroid gland, but further caudad. They are occasionally associated with the

inferior thyroid veins and esophagus, and may be placed in the thorax near to, or embedded in, the thymus. They have even been recorded as far caudad as the areolar tissue about the pericardium.

Both glands usually occur in association with the inferior thyroid arteries, which constitute the best clews to their location.

Blood Supply.—Each gland is supplied by a special branch from the inferior thyroid artery, which, after penetrating the capsule, breaks up into numerous branches, which ramify in the connective tissue framework

Fig. 2. Diagram of median sagittal section of a human embryo showing position of gill clefts, after Bailey and Miller, modified.

of the organ. The blood is returned through the capillaries into a venous plexus on the surface of the gland, which communicates, in turn, with the thyroid veins. Detailed accounts of variations in blood supply are given by Kohn (*b*), by Halsted and Evans, and by Pool and Falk.

Lymphatics.—The lymphatics have not been studied in detail, but it is clear that they are intimately associated with those of the thyroid gland, the lymph of the two glands intermingling.

Innervation.—The nerve supply from the perivascular sympathetic plexuses is very scanty and apparently escaped observation until the recent work of Rhinehardt. The exact mode of termination of the fibers is not definitely known; some of them, however, are certainly vasomotor in nature. Fibers ending on and between the gland cells have been recorded. As contrasted with the thyroid, the innervation is relatively scanty.

Embryology

Origin.—The parathyroid glands develop as thickenings of the endoderm of the third and fourth branchial clefts. These clefts are illustrated in Fig. 2, as seen from the inner surface of the pharynx of a human embryo. Their derivatives are indicated diagrammatically in Fig. 3. The superior parathyroids (marked with vertical lines) develop from the

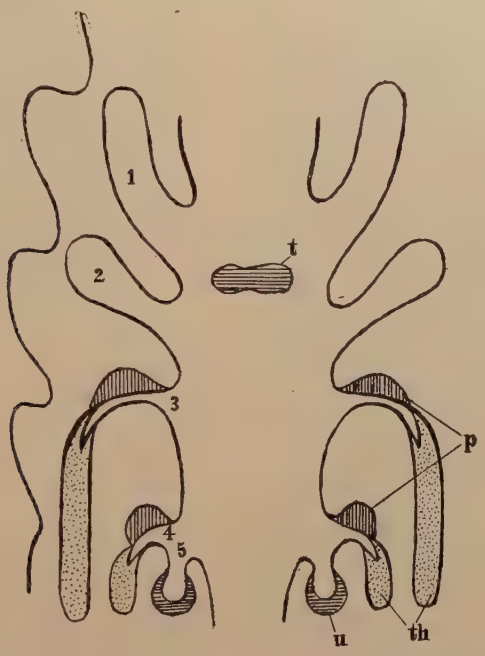


Fig. 3. Diagram showing derivatives of branchial pouches: thyroid (t) and ultimobranchial bodies (u) in horizontal lines, parathyroids (p) in vertical lines and the thymus (th) dotted, after Grosser, modified.

fourth cleft and are for this reason sometimes termed the glandulæ parathyroideæ IV. The inferior parathyroids (marked in the same way) arise from the third cleft and are called the glandulæ parathyroideæ III.

It will be seen that there has been a reversal, for the superior parathyroids (IV) are developed from the fourth pouch, yet they are located anteriorly to the glandulæ parathyroideæ III. This has been brought about by the fact that in the general caudal migration of the branchial derivatives, the thyroid and the glandulæ parathyroideæ IV have been outdistanced.

Growth.—The growth phenomena of the parathyroid glands have not been carefully studied, even in animals. Sexual variations are unknown in man. The glands appear, however, to be relatively larger in female

rats, and in this respect resemble the suprarenals and hypophysis (Jackson). The same author has also found that in the white rat their growth energy exceeds that of the thyroid; for in young white rats, held at main-

Fig. 4. Lateral lobe of the thyroid gland with included parathyroid (p) of normal white rat, after Jackson.

Fig. 5. Lateral lobe of the thyroid gland with included parathyroid of young white rat held at maintenance of body weight by underfeeding, after Jackson.

tenance of body weight through underfeeding for three weeks, the parathyroids actually continued to grow and increase in size, while the amount of thyroid tissue suffered a marked reduction. Compare Figs. 4 and 5.

Comparative Anatomy

Comparative anatomy sheds no light upon our understanding of the parathyroid glands. With the exception of the fishes, they are represented in all the classes of vertebrates, and everywhere are characterized by their extreme variability. Their variation in structure in the different domestic animals is discussed by Vermeulen. A study of the parathyroid body weight ratio in different classes of animals is much needed.

Histology

Histologic Morphology.—The parathyroids possess a capsule of fibrous connective tissue. The glandular cells within the capsule are disposed in

columns or clumps, separated, to a greater or lesser extent, by bands of connective tissue, which are continuous with the capsule.

Considerable variation is met with in the grouping of the gland cells, even in different parts of the same organ. Sometimes they form an almost solid mass with but little interstitial tissue; occasionally, however, the reverse is true. Quite frequently the cells show a tendency to group themselves into well defined follicles, as in the thyroid gland, which may even contain colloid substance; or it may happen that colloid material is distributed between cells not so arranged. The relation of this colloid to the colloid of the thyroid gland is not well understood. According to Schafer, it does not contain iodin.

Fig. 6. Human parathyroid. Note the close association of the cell columns with the blood vessels (magnification 720).

Cytology.—Two types of glandular cells are usually recognized in the parathyroids, the principal cells and the oxyphil cells. The principal cells are by far the more numerous, making up the mass of the tissue, and are characterized by their clear cytoplasm and faintly staining nuclei. The cytoplasm of the oxyphil cells, on the other hand, stains strongly with eosin and their nuclei intensely with hematoxylin. They have a pyknotic appearance and are generally thought to be undergoing degeneration in the later stages of cytomorphosis, similar to that of the colloid cells of Langendorff in the thyroid. This idea is supported by the fact that they do not make their appearance until nine or ten years of age.

Cell Inclusions.—Glycogen is found in both types, but rather more abundantly in the principal cells. It has also been described between the cells. Fat is deposited within the cells during the first month after birth and increases in amount with age. Mitochondria have been described in the principal cells by Bobeau (*a*) (*b*), who claims that they are transformed into secretion. He bases his conclusion entirely upon a correspondence in the distribution of the mitochondria and certain lipoid-like droplets in the cells. He demonstrated the mitochondria by methods which he does not specify, and the lipoid by the method of Ciaccio. He assumes that the lipoid droplets constitute a precursor of the secretion, or rather the secretion itself, and that they arise through a swelling up of the mitochondria.

Mode of Secretion.—True secretion antecedents remain to be discovered. We have convincing evidence that the glands do form something since removal, or mere ligation of their blood vessels, causes tetany and other characteristic symptoms, which are to some extent relieved by the injection of parathyroid extracts. Young animals are more susceptible than old ones and certain species more than others.

Preparations made by Fano's new (1920) cobalt and silver nitrate method reveal the fact that the reticular apparatus exhibits great variability in its cytoplasmic location, from which we may conclude that the cells are not definitely polarized for secretion in one direction (see thyroid section). Only when the parathyroid cells become grouped in clumps is there an assumption of secretory polarity as indicated by the reticular apparatus taking up a position between the nucleus and the discharging pole.

The ground substance in the cell, in which we can see no structure, is the active agent in almost all vital manifestations, including secretion. It is not homogeneous, however, because heterogeneity is prerequisite to activity. It is organized so as to permit of combination and isolation of chemical reactions, just as a factory is organized in space; but the mechanism of the organization in the cell is almost wholly unknown. Indeed, it cannot be too strongly emphasized that the absence of visible secretion antecedents does not mean that they do not exist. This is one of the limitations of anatomical evidence. In order to touch on fundamental vital processes, we must extend our views to include a study of the morphology of the ultramicroscopic.

Functional Relation to Thyroid.—Some investigators are of the opinion that the parathyroids are very closely related anatomically and physiologically to the thyroids, especially to the intervesicular cells already referred to in the section on the thyroid. Changes in the parathyroids, characterized by the formation of vesicles containing colloid after thyroidectomy, have been frequently described, though Vincent has recently expressed doubt regarding them.

The chief differences between the two glands are as follows: (1) In congenital atrophy of the thyroids the parathyroids are usually well developed, indicating a different manner of growth. Jackson has found that their growth energy exceeds that of the thyroid. (2) According to Ott's observations, as yet unconfirmed, extracts of the two have totally different physiological effects (citation from Schafer). (3) Their removal produces different symptoms, which even show a tendency to be antagonistic. (4) Iodin in any considerable amount is absent from the parathyroids. The claims which have been made, to the effect that thyroidectomy is followed by enlargement of the parathyroid glands and the deposit of colloid substance within them, are very difficult to substantiate.

Variations.—From the cytological point of view, the parathyroid glands have been so neglected, owing perhaps to the difficulty of studying

them in small laboratory animals, that we know practically nothing of the structural changes which they may undergo in different experimental conditions. It would be interesting and important to find out whether they respond, in the same way as the thyroid gland, to variations in diet, temperature, unhygienic conditions, etc.

Like the thyroid gland, and probably for similar reasons the parathyroids show the widest variations in structure, so that the interpretation of our histological findings is very difficult. At present, there are no known histological criteria on which we may, with confidence, gauge the activity of the parathyroid glands.

Physiology, Physiological Chemistry and Experimental Pathology of the Parathyroid Glands. . . . . .

. . . . . *Sutherland Simpson*

Introduction—Experimental Pathology—Earlier Observations—Observations after the Discovery of the Parathyroids as Independent Entities—Difference between Thyroid and Parathyroid Manifestations—Discovery of the Internal Parathyroids and Subsequent Experimentation—Investigations as to the Indispensability of the Parathyroids—Studies on the Comparative Anatomy—Investigations as to the Relationship between the Thyroid and Parathyroids—Evidence that Parathyroidectomy May Produce No Symptoms—Accessory Factors in the Results of Parathyroidectomy—Symptoms of Tetania Parathyreopriva—Relation of the Nervous System to Parathyroid Tetany—Experimental Attempts to Augment or Allay Parathyroid Tetany—The Relation to Metabolism—Intoxication Theory of Parathyroid Tetany—Physiology—Chemistry—Summary.

Physiology, Physiological Chemistry and Experimental Pathology of the Parathyroid Glands

SUTHERLAND SIMPSON

ITHACA

Introduction

In attempts by physiologists to determine the functions of any of the endocrine organs or glands of internal secretion, two general methods are employed.

One is to study the effects, immediate or remote, of the surgical removal of the organ in the lower animals, or of its destruction, by accident or disease, in man; the other is to observe what happens when the gland itself, or a watery, saline, or alcoholic extract of it, is administered intravenously, subcutaneously, or by mouth.

The results obtained by either of these methods must be interpreted with caution, however, since it must be remembered that the effect of suddenly removing an organ in toto may be quite different from that of its gradual disappearance in disease. Because a certain action follows the administration of an extract of any particular gland, it does not necessarily follow that this gland, in situ, is continuously furnishing an internal secretion which normally brings about this action; the extract with which we are dealing may be a postmortem product. In the case of the parathyroid gland, practically all our knowledge of its functions has been gained by an application of the first of these two methods; the second has yielded, so far, little or nothing.

In several cases the attention of the physiologist was first attracted to the organ in question by the clinician. The relationship established by the physician Addison between certain pathological changes in the suprarenal capsules and the group of signs and symptoms first described by him, marked the starting point of the investigations of physiologists into the functions of this organ. The same may be said of earlier studies in the case of the thyroid and pituitary glands. With regard to the parathyroids, however, the order has been reversed. The knowledge gained by the physiologist, mainly as the result of experimental extirpation, has led

the clinician, rightly or wrongly, to associate these glands with the various forms of tetany and allied conditions.

Experimental Pathology

Earlier Observations.—The earliest recorded experiments on animals bearing on the physiology of the parathyroids are those of Raynard in 1834-35. In the operative treatment of goiter in dogs he states that the thyroid gland may be removed in old animals with great advantage; the operation is frequently successful in dogs of medium age, but in pups, up till the second or third month, it ends fatally within a few days. As we now know, it was the loss of the parathyroids that must have been responsible for the death of these animals.

V. Rapp in 1840 stated that in removing the thyroid gland in goitrous dogs the animals frequently died a few days after the operation.

Schiff (*a*) (1859) was the first to attack the problem seriously from the experimental side. He removed the thyroids from a number of animals of different species—rabbits, rats, guinea pigs, dogs, fowls—and found that, while many survived, several dogs, a cat, and a rat died within a few days. He does not describe the symptoms before death, except to say that the dogs showed a distinct hesitation in their movements. In his description Schiff quotes Lacauchie as having produced violent symptoms in dogs which died within twenty-four hours of the removal of one lobe of the thyroid gland. This is probably the earliest account of postoperative tetany in the literature.

In 1884, stimulated by the clinical observations of Reverdin, Kocher, and others, Schiff (*b*) again gave his attention to the subject. In the early eighties, when the principles of Lister had rendered surgical operations comparatively safe, Kocher, Reverdin, and Billroth were induced to remove goitrous glands in the human subject, for the simple purpose of getting rid of the physical deformity. At that time the existence of the parathyroids was unknown, except to Sandström, who first described them in 1880, and the few people who had happened to read his paper, and the thyroid was not believed to have any important function, hence no serious consequences were anticipated from its removal. In several cases, however, acute nervous symptoms followed, and it was, no doubt, the widespread interest taken in these results at the time that led Schiff to return to the subject of thyroid extirpation in animals, which he had abandoned many years previously.

Schiff was a pioneer in many fields. In 1884 he published a report of his investigations. In the rat and rabbit no symptoms followed the removal of the gland. In the dog and cat, on the other hand, the result was almost invariably fatal. Of sixty dogs, the great majority died with acute

nervous symptoms within the first week after the operation. Only one remained alive at the end of the fourth week, and this single survivor succumbed in fifty days. Schiff also found that if, previous to removing the thyroid, he transplanted into the peritoneal cavity the thyroid gland of another animal of the same species, no symptoms followed.

These experiments of Schiff mark the beginning of the scientific study of the functions of the thyroid and parathyroid glands, and it is only since the time of these observations that any real advance has been made.

The observations of Schiff were confirmed by Wagner (1884), who studied the nervous and muscular disturbances in cats particularly, and is stated to have been the first to report an increase in the excitability of the peripheral nerves to the galvanic current. Colzi (1884) and Sanquirico and Canalis (1884) also reported similar results.

Horsley (*a*) in 1885 described the nervous symptoms as they appeared in dogs and, more particularly, in monkeys, which he was the first to employ in this work. According to his account, the monkey, as a rule, appears perfectly well for about five days after complete removal of the thyroid. Then there is noticed a slight fibrillation of the intrinsic muscles of the hands, feet, and jaws, following this order in successive invasion. As a rule, the fibrillation soon becomes a constant tremor, to which is then added a series of powerful clonic spasms. This paroxysmal stage usually appears about the second or third day after the tremors are first noted and persists for about twenty days. The spasms gradually fail in force, reassume the type seen at their onset and disappear, sometimes as long as ten days before death. These nervous symptoms were less severe in the monkey than in the dog.

In 1891 Horsley (*e*), summing up the results of his work begun several years before, divides animals into four classes as regards the results which follow complete thyroidectomy. According to this classification, birds and rodents show no ill effects. In the ungulates—sheep, goat, donkey, pig—the symptoms develop very slowly; there is a general cachexia, which finally, after many months, results in death. In the third class, in which he places man and the monkey, the effects are more severe; myxedema is a marked feature, with increasing cachexia, which ends in death. In the carnivora removal of the gland is followed, in a few days, by acute nervous symptoms, characterized by severe tetany and convulsions, with an early termination. These results appeared to point to the conclusion that the food habits of the animal have much to do with the effects which follow thyroidectomy. The purely carnivorous animals, such as the dog and fox, are most severely affected, the herbivora scarcely at all; while the omnivora, living on a mixed flesh and vegetable diet, occupy a middle position.

The observations of Breisacher, who found that dogs which were fed on meat before and after thyroidectomy suffered more severely and succumbed sooner than those fed on milk, seemed to support Horsley's conclu-

sions. It was the generally accepted belief, at this period, that the determining factor was metabolic.

Observations After the Discovery of the Parathyroids as Independent Entities.—The external parathyroids were discovered by Ivar Sandström in 1880. He found these bodies constant in fifty autopsies in man, and he also studied and accurately described their position and structure in the dog, cat, rabbit, ox, and horse; nevertheless, his work was lost sight of, and in extirpation experiments on the thyroid no cognizance was taken of these bodies. It was not until their rediscovery by Gley (*a*) in 1891 that they received the attention of physiologists.

The work of Gley may be said to mark the beginning of the second epoch in the history of the physiology of the parathyroid glands. Prior to this, the effects which we now believe to be due to absence of parathyroid tissue were ascribed to thyroid deficiency. In 1892 Gley (*b*) published several papers describing the results of his experimental work on the parathyroids. In the rabbit he found two glands, one on each side, some distance below the lower pole of the lateral lobe of the thyroid. Their location was such that previous workers, unaware of their existence, in removing the thyroid, had, in all probability, left them untouched. In the dog, on the contrary, the glandules were found closely applied to the external surface of the lateral lobe of the thyroid and within its capsule, so that here they must always have been removed along with the thyroid lobes. As Gley understood it at that time, two quite different operations had been performed by his predecessors in this field; in the one case (rabbit) simple thyroidectomy, in the other (dog) thyroparathyroidectomy.

Difference Between Thyroid and Parathyroid Manifestations.—In his first series of experiments Gley removed both the thyroids and parathyroids from sixteen rabbits. Fourteen of these were seized with acute symptoms, which began one day after the operation and proved fatal within a few hours. In the light of subsequent experiments on this animal, this seems to be an unusually large proportion. When he removed the parathyroids and left the thyroids untouched, and, vice versa, when the thyroid lobes were taken away and the parathyroids left behind, no acute symptoms followed. He also showed that in the dog, when he removed the thyroid, taking care to leave behind the two parathyroids, the animal showed no immediate ill effects. At the time of his earlier experiments Gley was not aware of the existence of the internal parathyroids; these were described, for the first time, by Kohn (*a*) in 1895.

The explanation offered by Gley for the difference which all previous workers had found in the effects following so-called thyroidectomy in the carnivora and herbivora, respectively, were based, not on the character of the metabolic processes of the animal, but on purely anatomical grounds. In the carnivora the operation was complete, all the thyroid tissue having been removed; in the herbivora, on the other hand, some, in the form of

the parathyroid glandules, had been unintentionally left behind and the operation was incomplete. At this period Gley held the opinion that the parathyroids represented embryonic thyroid tissue, which undergoes hypertrophy and develops into functionally active thyroid after that gland has been removed; in other words, potentially embryonic thyroids. In this he was probably influenced by the description of these organs given by Baber (1880).

These important researches of Gley, begun in 1891, were continued by him and his pupils for a number of years, and the results are embodied in a series of papers published, for the most part, in the Comptes Rendues de la Société de Biologie, from 1891 to 1897 and later. Soon after his first publication many other workers were attracted by this fascinating problem and our knowledge of the subject became greatly extended. Gley's ideas on the importance of the parathyroids were supported by some and denied by others.

Moussu (*a*) (1892) repeated the experiments of Gley on the rabbit, and of eleven adults so treated none succumbed. Considering these negative results, this author refused, at that time, to recognize the important rôle assigned to the parathyroids by Gley.

Hofmeister (*b*) (1894) did not admit that the parathyroids left in situ at the operation either increase in size or become modified in structure in any way. In young rabbits, he concluded, extirpation of the thyroids alone gives rise to typical cachexia, which runs a chronic course, while simultaneous ablation of the parathyroids leads to fatal tetany.

This transformation of the parathyroids left behind into thyroid tissue was also denied by Vassale and Generali, and later (1895) Gley himself, in association with Nicolas, on further experimentation, failed to find any such change.

Discovery of the Internal Parathyroids and Subsequent Experimentation.—The next important advance was made by Kohn (*a*) in 1895 when he discovered that in addition to the glandules described by Sandström, Gley, and others, there were two additional and similar bodies embedded in the substance of the thyroid lobes. These are now usually known as the internal parathyroids. According to Kohn, every animal is provided with four parathyroids, arranged in two pairs, an internal pair imbedded in the substance of the thyroid, and an external pair, situated at some distance from the thyroid in the herbivora, but in the carnivora lying on the surface of that gland and usually within its capsule. This observer insisted that the parathyroids are organs anatomically separate and functionally distinct from the thyroid. Later, as the result of a more extensive investigation, he was confirmed in his original opinion and demonstrated the separate embryological origin of the thyroids and parathyroids.

The Italian observers, Vassale and Generali (*c*) (1900) were the first, from the experimental side, to avail themselves of this additional anatom-

ical knowledge. They studied serial sections of the thyroid in the cat and dog, and became thoroughly acquainted with the topographical positions of the four parathyroids in these animals. They then proceeded to extirpate both internal and external "epithelial corpuscles" in nineteen animals—ten cats and nine dogs. Of the cats so treated, nine succumbed within ten days, most of them about the fifth day following the operation. They presented a typical morbid syndrome, viz., fibrillary contractions and muscular spasms, psychical depression, rigid and uncertain gait, anorexia, tachycardia, rapid emaciation, fall in body temperature, and death. One of the cats, operated upon on January 5, 1896, was still alive when the paper was written in March of the same year, but it was greatly emaciated and in a state of chronic cachexia.

Of the nine dogs included in the research, all perished within eight days, most of them on the third or fourth day after the operation. They were in good condition on the day following the operation; they began to show symptoms on the second or third day, and died shortly after. Involving the nervous system, there were tremors, psychical depression, paresis of the muscles of mastication, trismus, rigidity of the hind limbs, uncertain gait, general muscular weakness, slight convulsions, and then, most frequently, death. There were loss of appetite and vomiting, indicating disturbances of the digestive system, palpitation and dyspnea; the urine was very scanty and sometimes showed traces of albumin.

The symptoms, the observers concluded, which follow the removal of the four parathyroid glands are analogous to those which result in the cat and dog from complete thyroidectomy, that is, the simultaneous removal of the thyroid and all parathyroids. They draw attention to the fact that, in their experiments, the acute convulsive symptoms were not accentuated, but, on the contrary, that there was evidence of diminished excitability of the nerve centers, ending in a rapidly fatal paralysis. At the postmortem examination was found slight congestion of the liver and kidneys and, in some cases, a certain degree of anemia of the nervous system, but nothing specific to point to the cause of death. Nothing in the operation, as such, could account for the fatal termination. There were no complications and no involvement of the thyroid itself, nor of the nervous structures in the vicinity. In most of the animals the wounds healed by first intention; in the cats, indeed, there was frequently complete cicatrization. The external parathyroids were enucleated with scarcely any injury whatever to the thyroid, and in taking away the internal parathyroids with curved scissors, especially in the cats and dogs, very little thyroid tissue was removed along with them. No change was found in the thyroid, except that in some cases colloid material was absent from the intraglandular and periglandular lymphatic spaces. With regard to the possibility of nerve lesions giving rise to the symptoms, these could not be greater, they concluded, than would be produced by complete thyroidectomy.

Further, to prove that the parathyroids were responsible for the after effects and not any damage to the thyroids, in one dog they removed two small portions of each lobe of the thyroid, leaving the parathyroids intact; no symptoms followed. One circumstance which seemed to surprise them was that death appeared to follow more certainly and more rapidly than after the complete thyroparathyroid operation.

In a further communication, in discussing various hypotheses to explain the results of simple parathyroidectomy, Vassale and Generali draw attention to the fact that Lusena had confirmed their statement that extirpation of the parathyroids alone is more rapidly fatal than thyroparathyroidectomy, and, further, to his observation that, when a dog is in tetany following parathyroidectomy, removal of the thyroid will bring about an improvement in his condition. Vassale and Generali were able to corroborate this last point in the case of two of their own experimental animals. Le Play later has denied this, and many others corroborate him. To explain their observations on this point, Vassale and Generali put forward the theory that the parathyroids have an antitoxic function, while the thyroid stimulates metabolism. An animal deprived of its parathyroids is a poisoned animal. If the metabolic processes are active, as they will be if the organism possesses a thyroid, this poison will be produced in greater quantity; if less active, as in animals deprived of their thyroids, it will be produced in less quantity. Hence, when an animal is suffering from parathyroidectomy, one might expect an amelioration of the symptoms after the thyroid is removed. This theory, they argue, is supported by the following facts: Parathyroidectomy is less serious and runs a milder course in old than in young dogs; it is extremely severe in dogs that eat heavily, particularly of meat; in fasting animals the symptoms are much less severe; in parathyroidectomized dogs the neck wound heals readily by first intention, without any special antiseptic precautions being necessary, whereas, in thyroparathyroidectomized animals it frequently becomes infected.

The work of Vassale and Generali was repeated and extended by several investigators, and about this time a controversy arose, first, as to whether the parathyroid glands are essential to life in all classes of animals, and second, regarding the physiological relationship between the thyroid and parathyroids.

Investigations as to the Indispensability of the Parathyroids.—Blumreich and Jacoby (1896) concluded that there is no great difference between the effects of thyroidectomy and those of parathyroidectomy.

Munk (1898) strongly opposed the theory that the parathyroids are "vitally essential." In a summary of his work up to 1898 it is stated that about fifty per cent of his monkeys and rabbits and twenty-five per cent of his cats and dogs were not affected by the operation. Notwithstanding the assertions of Vassale and Generali, and of others to the contrary, he

was inclined to attribute many of the symptoms that follow interference with these glands, in the hands of other experimenters, to damage done to the nerves of this region.

Edmunds (1902), on the other hand, using dogs and monkeys, came to the opposite conclusion. He made complete and partial extirpations of the thyroid and parathyroids and decided that the acute symptoms are caused by the loss of the latter. He states that, if one thyroid lobe and two-thirds or more of the other be removed, the animal will live, provided one parathyroid be included in the part of the thyroid left behind; otherwise it will die. He also noted that the palpebral fissure becomes narrowed after parathyroidectomy. Several of his animals survived the complete operation, and, as the existence of accessory parathyroids was not suspected at that time, he was at a loss to account for this. He failed to find any change in the parathyroid glands of the rabbit left behind at the operation.

Kishi (1904) obtained varying results with different animals. Of twenty-four dogs, only seventeen died within periods ranging from four to fifty-one days after operation, most of them in the first two weeks; and of twelve cats, all were dead within a fortnight except one, in which he had left behind a single parathyroid; that animal showed no symptoms whatever. In monkeys he had only one death out of six in which the operation was done, while in rabbits there were three out of three. In the case of two goats, one died in thirteen days and the other in six months. No statement is made with regard to the age of the goats, but, as the first had a body weight of 7.5 kgm. and the second of 13.16 kgm., age probably had some influence. The number of dogs which survived the complete operation in Kishi's series, while 100 per cent of the rabbits succumbed, is remarkable.

Rouxeau (1897) believed that the parathyroids were very important organs. He removed these in twenty-one rabbits, leaving the thyroids behind, and all but three died of acute symptoms, in every respect the same as those that followed complete thyroparathyroidectomy.

Moussu (*d*) (1897), after experimenting upon cats, rabbits, and dogs, came to the conclusion that the thyroid and parathyroids have distinct and separate functions. The loss of the thyroid is followed by chronic disturbances of metabolism leading to myxedema and cachexia, while absence of the parathyroids produces acute symptoms and early death. Of fifty-five dogs, on which he performed the complete operation, thirty-three died early of acute symptoms, and in the case of the others, their survival in many instances was explained by the finding of one or more parathyroids, post mortem, which had inadvertently been left behind.

Christiani (*a*) (1893), after removing both thyroids and parathyroids in the rat, reported that most of the animals so treated died in tetany shortly after the operation.

Capobianco and Mazzioti (1899) found that removal of all parathyroids is invariably fatal.

Welsh (*a*) (1898) carried out a series of partial and complete removals of the parathyroids in the cat, and found that acute and severe symptoms followed, although the thyroid remained practically intact. With only one of the glands left in some cases, the animal was unable to survive. He saw no evidence of the transformation of parathyroid into thyroid tissue, and considered that there is no functional relationship between the two.

Pineles (*a*) (1904) reported that in the monkey the symptoms are, as a rule, more chronic than in the cat or rabbit. In his experiments the parathyroids were taken away in two or three stages; nothing happened until the last glandule was removed, when death by tetany resulted. The loss of three parathyroids, as a rule, gave rise to no acute symptoms. In his cats, from which all parathyroid tissue had been removed, the average duration of life was five and a half days. As the result of his own experiments, Pineles concluded that the acute tetanic symptoms and early death are due to loss of the parathyroid glands, while the chronic changes and trophic disturbances arise from thyroid deficiency.

Doyon and Jouty claim to have produced fatal results by removing all the parathyroids in birds. The writer has attempted to extirpate the thyroids and parathyroids in chickens, and found the operation so difficult that he was compelled to abandon the attempt. Doyon and Kareff obtained similar results in the turtle.

Erdheim (*e*) (1911) did some very careful work on the rat. This animal is said to possess only two (both external) parathyroids. In twenty-nine animals, both glands were destroyed by a fine electrocautery and in twenty-seven of these tetany appeared in from three to seven days. If only the half of one parathyroid was left, either no effect at all followed or only very mild symptoms, and in some cases slight indications of tetany were seen after the removal of a single gland. In eight rats, a part of the thyroid was removed without injury to the parathyroids, and in those cases no signs of either acute or chronic symptoms appeared. Erdheim believed that trophic symptoms may result from partial loss of the parathyroids. It is important to note that he made serial sections of all the neck organs post mortem, and proved conclusively that whenever the parathyroids were entirely absent, no matter whether the thyroid was present or not, the animal showed acute tetany. Usually symptoms appeared within the first twenty-four or thirty-six hours, and these consisted of muscular tremors and disturbances of various kinds, ending often in the status epilepticus. It is interesting to compare this result with that of Vincent and Jolly, who state that "the thyroids and parathyroids may be destroyed or removed without affecting the animal (rat) in any way." It is within the limits of possibility that both statements may be correct. Much de-

pends upon the general condition of the animal at the time of the experiment.

Erdheim also noted changes in the enamel of the teeth when the animal lived sufficiently long to show these. He ascribed this to a lack of calcium in the growing tissue, but this aspect of his work will be considered later.

Studies on the Comparative Anatomy of the Parathyroids.—Following the publication of Kohn's paper, a great many investigators made careful studies of the comparative anatomy of the thyroid and parathyroid glands in many different species. Their anatomical relations were investigated in the following animals:—dog, cat, man, rabbit, horse, ox, guinea pig, monkey, fox, goat, pig, seal, bat, rat, mouse, and some birds. Most observers agree that the parathyroids are four in number, two internal and two external glands, except in some species, such as the rat, in which only two are present. So constant, indeed, was the number supposed to be, that Groschuff made the suggestion that mammals might be classified in two groups, according to whether the species possessed two or four parathyroids. Occasionally an accessory gland was reported, but four parathyroids were generally regarded as the greatest number ever present. It is important to keep this in mind when one considers the results of extirpation experiments reported during this period.

Rogers and Ferguson (1906) examined microscopically 253 "suspicious pieces" of tissue removed from human adults, infants, dogs, and horses, and found only 36 per cent of these bodies to be parathyroids, while 42 per cent consisted of thyroid tissue, in spite of the fact that these nodules were selected "because of a resemblance to parathyroid." The remaining 22 per cent consisted of lymphatic glands, thymus, vascular connective tissue, and mucous gland.

Moussu (*b*) (1896) had noted the occurrence of supplementary thyroids in the dog, but Jeandelize (1903) doubted their existence.

Schaper (1895) stated that in the sheep he has very often found nodules of a parathyroid structure near the bifurcation of the common carotid, and others—two, three or more—along the course of this artery. Jeandelize has confirmed this in the sheep.

Forsyth (*b*) (1908) made an extended research into this subject, using forty-two mammals and thirty-five birds of many different species obtained from the Zoölogical Gardens in London. The method of procedure was as follows: Every glandular body was removed from the neck and subjected to careful microscopic examination. The thyroid itself, if small, was examined by serial section, but, if large, was cut into thin slices, the surfaces of each slice being carefully scrutinized with a lens and all suspicious looking pieces retained for microscopic examination. "In brief, the guiding principle followed was to regard every gland as a possible parathyroid, and none has been identified except by its microscopical features."

This detailed research led to conclusions at variance with the previously accepted belief in the constancy of number of parathyroids in each species. For example, in three specimens of the green monkey (Cercopithecus callitrichus) examined, the parathyroids numbered one, one, and eight, respectively. Although, in the majority of cases, only four are found, still the parathyroids frequently vary in position and number in different species, and in different members of the same species. Further, the existence of parathyroid tissue in the thyroid, not isolated by connective tissue, was found to be of much commoner occurrence than was anticipated. Forsyth goes on to say that "intermediate types" (between thyroid and parathyroid structurally) are readily found both in the thyroid and in accessory glands, with the result that the identity of some bodies has often presented difficulty. "Under these circumstances it might have appeared undesirable to retain the two expressions thyroid and parathyroid; but, since the histological distinction between the two is widely recognized and is a convenient one, it was found advantageous to employ both in the following descriptions. The usage is not to be taken as an assent to the proposition that there is functional difference between the thyroid and the so-called parathyroid glands."

At this time, as we have seen, the great majority of workers agreed with the teaching of Gley and of Vassale and Generali, viz., that removal of all the parathyroids from an animal, even if the thyroids be left intact, invariably leads in a few days to the death of the animal from acute nervous symptoms commonly known as tetania parathyreopriva, while extirpation of the thyroid alone gives rise to chronic symptoms analogous to those of myxedema in man—postoperative myxedema or cachexia strumipriva. It was held that the two organs are distinct and independent structurally, embryologically, and functionally, and, as regards vital importance, the thyroid is secondary to the parathyroids.

Investigations as to the Relationship between the Thyroid and Parathyroids.—In 1904 Vincent and Jolly published the results of an extensive investigation into the physiology of the thyroid and parathyroids. They used cats, dogs, foxes, monkeys, rats, guinea pigs, and rabbits in their first series, and monkeys, cats, dogs, prairie wolves, badgers and rats in their second. In their operations they experienced considerable difficulty in separating the two glands. These difficulties, mainly anatomical, they say, had been understated by previous workers. In speaking of the removal of the internal parathyroids, Vincent says: "When it is remembered how vascular the thyroid tissue is, how slightly the parathyroid differs from it in appearance to the naked eye, and how this difference, slight as it is, entirely disappears when there is any bleeding, it will be seen that the operation of digging out the internal parathyroid is one of extreme delicacy. A further difficulty presents itself in the fact that there is a nodule of thymus also imbedded in the thyroid lobe, frequently in

close proximity to the internal parathyroid, resembling it on the naked eye examination, and therefore easily mistaken for it in the course of the operation." Bearing all these difficulties in mind, these observers do not hesitate to declare that, except in very favorable cases, in which the internal parathyroid chances to lie near the surface of the thyroid lobe, the operation is an impossible one. The injury caused to the thyroid by attempts to enucleate the internal parathyroids, they believe, may be held to account for the deaths of many animals in the hands of other experimenters, which at the time were attributed to parathyroid insufficiency. To remove all thyroid tissue, leaving the parathyroids, particularly the internal pair, with their blood supply undamaged, they regard as still more difficult.

In their experiments on cats, when one thyroid lobe was left and one parathyroid, or two thyroid lobes with one parathyroid, the animals remained perfectly well. When parathyroids alone were left, out of five cases, one proved fatal. When the thyroid was left and all four parathyroids successfully removed, only 33 per cent proved fatal. One of these did not show typical symptoms, and in the other two fatal cases, the thyroid gland was found at the postmortem examination to be extensively damaged. "In the great majority of cases no ill effects of any kind resulted from the operation." Simple parathyroidectomy in the cat, when the thyroid is left unimpaired, is not necessarily fatal. Their fatal cases were those in which they had done most damage to the thyroid. This was directly opposed to the prevailing view.

Out of five dogs, the complete operation in one produced no symptoms, and in this case no accessory parathyroids were found later when the animal was killed.

In foxes symptoms appeared within five hours in two cases, and probably in a third, and death soon supervened. Foxes were the most purely carnivorous animals employed.

In monkeys removal of the parathyroids together with the thyroids did not prove fatal, although in some cases transient nervous symptoms were observed. In these animals, according to Vincent and Jolly, neither the thyroids nor the parathyroids are essential to life.

In the rat thyroid and parathyroids may be destroyed without affecting the animal in any way. In guinea pigs similar results were obtained, but in rabbits the matter was doubtful.

As determining the result, they seem to attach great importance to the metabolic habits of the species. The variable effects produced in different animals cannot be explained on anatomical grounds, nor are they probably due to mere variations in feeding, but rather to deep seated physiological conditions.

In their second paper (1905) they confirm their former findings and, in addition, make the statement that such a carnivorous animal as the

badger is totally unaffected by the complete removal of the thyroid and parathyroid glands.

Their final conclusion is, in part, as follows: "Neither thyroids nor parathyroids can be considered as organs absolutely essential to life. . . . When parathyroidectomy proves fatal, this is probably due to the severe damage done to the thyroid, and it is possible that there may be a difference between the results of severe damage to the thyroid apparatus and its total removal. Thyroids and parathyroids are to be looked upon as a single physiological apparatus, the two kinds of tissues being intimately associated embryologically and working together physiologically. When the thyroid is removed, the parathyroids appear capable of functionally replacing it to a certain extent, and their histological structure changes accordingly." This seems to be essentially the original view of Gley, which he abandoned later.

Forsyth (*b*) (1908) appears to support the conclusions of Vincent and Jolly. In a review of the recent work on the subject, up to 1908, he sums up as follows: "Restricting our attention to these observations on the parathyroids which have led to fatal results, we find, in the first place, that only a percentage (varying from about 15 per cent to about 90 per cent) of the animals experimented upon die, or even develop symptoms, within a reasonable period. These figures are inclusive of every pathological development subsequent to the operation, yet a certain number of these results must be surely coincidental." He expresses the opinion that the parathyroids are glands essentially thyroidal in nature, possessing no peculiar function, but engaged in the active secretion of the same substance as the thyroid; they are, in fact, portions of the main thyroid gland which have assumed functional activity but have not yet formed vesicles; if, however, the thyroid be removed, they may develop into thyroidal tissue.

The conclusions of Vincent and Jolly and of Forsyth are contrary to the generally accepted doctrine, and few subsequent workers have supported them. Vincent has more recently (1920) expressed doubt as to the validity of his former view.

In 1911 Halpenny and Gunn—working in Vincent's laboratory in Winnipeg, repeated the experiments of Vincent and Jolly on monkeys, and the effects of the operation have been much more serious in their hands. All their animals, eight in number, with one exception, began to show symptoms very early—one on the third day after the operation, three on the fourth day, two on the fifth day, and one on the thirteenth—and in every case there was a fatal termination. One animal remained well until the seventy-first day, but died ten days later.

The opponents of Vincent and Jolly, of Forsyth, and of others who support them, explain the comparatively large number of cases that show no symptoms after removal or destruction of all four parathyroids in the hands of some experimenters as due to the presence of accessory parathy-

roids, which have been inadvertently left behind. Parathyroid tissue is said to occur frequently in the thymus. Harvier (1909) found it so in fifty per cent of all the cats he examined, and Marine (1914) in five or six per cent of dogs. Pepere (*b*) (1907), who upholds the theory of a separate and important function for the parathyroid, found small bits of parathyroid tissue in the thymus of nearly all rabbits.

MacCallum adheres to the theory of Gley and of Vassale and Generali that the parathyroids are vitally essential. He says: "At least we know well that the destruction of all the parathyroid glands results in the death of the animal with symptoms of tetany, which is not in the least dependent, as was once taught, upon the destruction of the thyroid gland." His own experiments and those of others have convinced him, beyond doubt or question, of the correctness of this view. Again, MacCallum and Voegtlin (1909) state that "the fact appears to be thoroughly well established, in spite of the dissenting voices of a few English investigators, that the parathyroid glands are organs of independent nature, and not developed from the thyroid or convertible into thyroid tissue. The evidence against this is of so insignificant a character, as compared with the overwhelming evidence in its favor, that space need not be occupied here in discussing it."

Paton and Findlay (*b*) say: "The clearest evidence that the structures are not identical is the fact that the removal of the parathyroids produces tetany, and removal of the thyroid does not do so; and this being the case, it seems unnecessary to give further consideration to a theory which has been amply refuted by adequate experimental evidence from many different sources. Our experience only confirms the conclusions arrived at by these former workers. Nothing can be more convincing than to remove all the thyroid tissue—along with the parathyroids—leaving one external parathyroid with its blood supply intact. Generally no symptoms at all, or at most transient tremors supervene, and only when the remaining parathyroid is removed does true tetany develop." It should be remembered that both MacCallum and Paton worked mainly with dogs and cats.

Evidence That Parathyroidectomy May Produce No Symptoms.—In the course of the last twelve years the writer has performed the complete operation on upwards of one hundred dogs, and, with one possible exception, in which no opportunity of observing the effect was available, every one of these animals was seized with the symptoms of acute, postoperative tetany within a few days after the operation (one in twelve hours); many of them died, and to the others the extirpation would probably have proved fatal, if they had not been purposely killed by an overdose of chloroform in the acute stage. This is probably an unusual experience, since there are few records in the literature of series of thyroparathyroid extirpations 100 per cent successful, judged by the fact that tetany always followed, even in the dog. In view of these results, he was perfectly convinced of the truth of the Gley theory, viz., that complete parathyroidectomy is always

fatal, and would have made a statement to that effect as positive as that of MacCallum or of Paton.

In 1911, however, the writer removed the thyroids, including the internal and the external parathyroids, from four lambs and four adult sheep. The lambs all showed acute symptoms shortly after the operation and died. In the case of none of the adult sheep were such results noted during the time they were under observation—three to four months. It might be said that failure to produce tetany in the four sheep was due to the fact that some accessory parathyroids had been overlooked at the opera-

Fig. 1. Sheep (right) from which both lobes of thyroid, including internal parathyroids, and two external parathyroids were removed on Nov. 20, 1919, and twin lambs born by this sheep on April 15, 1920. Photograph taken July 27, 1920.

tion and were not discovered at the autopsy. It would be a strange coincidence, however, if, by the same operator, all the parathyroids should be removed in the four lambs, in which, in fact, they are more difficult to find on account of the larger size of the thymus, and some left behind in each of the four adult sheep.

On November 20th, 1919, I performed the complete operation in four adult sheep; left both external parathyroids behind in a fifth, removing the thyroid, including internal parathyroids; and kept a sixth untouched as a control. Shortly after the operation all became pregnant, and two of the four which are believed to have lost all thyroids and parathyroids are alive, suckling lambs (one a pair) and to all appearance in perfect health at the date of writing, July 27, 1920, neither having ever showed any symptoms (see Fig. 1).

One, after dropping a dead fetus on April 2, showed signs of tetany on

May 24, and a tracing was obtained from it on May 25—six months after the complete operation—showing both the muscular tremors and larger clonic contractions characteristic of postoperative tetany (see Fig. 2).*

The fourth died on March 4—one hundred and five days after the operation—greatly emaciated, but without ever having shown any signs of tetany. At the postmortem examination two dead fetuses were found in utero. A careful search revealed no trace of either thyroid or parathyroid tissue. The fifth, with two external parathyroids left intact but both lobes of thyroid removed, died on April 4—one hundred and thirty-six

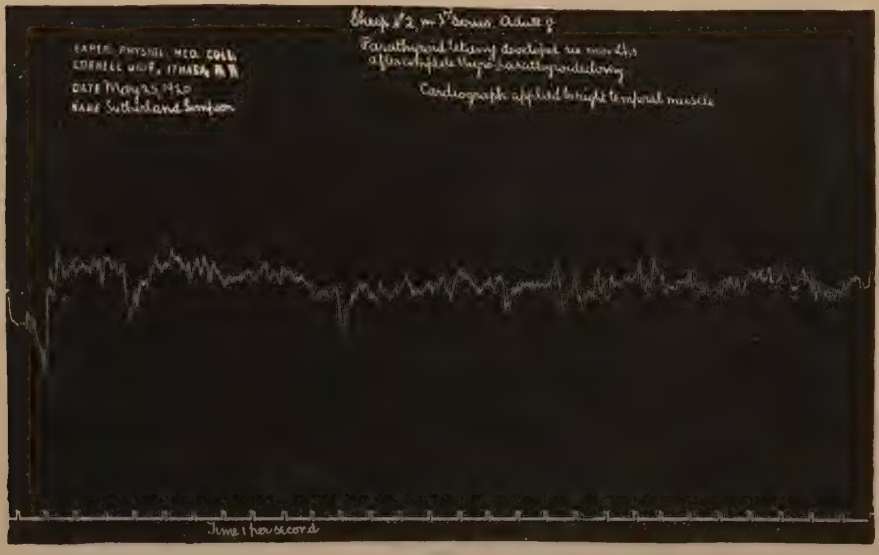

Sheep #2, ♀ Merino. Adult ♀
Parathyroid tetany developed six months after complete thyro-parathyroidectomy
Cardiograph applied to right temporal muscle
EASTERN PHYSIOL. MED. COLL.
CORNELL UNIV., ITHACA, N.Y.
DATE May 25, 1920
NAME Sutherland Simpson
1 sec record

Fig. 2. Tracing from temporal muscles of sheep in tetany 187 days after both lobes of thyroid, including internal parathyroids, and two external parathyroids had been removed.

days after the operation—of what the veterinary pathologist who conducted the autopsy described as "acute exudative rhinitis and pneumonia." A dead fetus at about full term was found in the uterus and there was also some hemorrhage and necrosis in the cotyledons of the placenta.

This ewe had not lost flesh. The control, which gave birth to a healthy male lamb on April 6, is alive and in good condition. The details of this experiment will be published later.

It is not improbable that certain conditions in body metabolism, not yet understood, have a determining influence on the results which follow

* Subsequent to the writing of this article, the ewe shown in the photograph was killed (Dec. 11th, 1920) and a careful search made for accessory thyroid and parathyroid tissue. Five suspicious pieces were removed from the neck and on microscopic examination three of these proved to be hemolymph nodes, and two, measuring 5x3x2 mm. and 7x5x4 mm., respectively, consisted of thyroid tissue. No accessory parathyroids were found.

removal of the parathyroid glands. If the latest theory advanced by Paton is correct, viz., that the symptoms of tetany are due to the accumulation of guanidin or some allied substance which follows suppression of the parathyroid function, it is quite conceivable that in certain classes of animals, and under certain conditions, this poison might not be produced in sufficient quantity to cause harm, or that the bodily mechanism might quickly adapt itself to the altered conditions, so as to bring about its destruction by some agent other than the vital activity of the parathyroid glands. Until we have more exact information concerning the rôle played by the parathyroids, it is premature to assert positively that in all mammals they are essential to life, and that, if, after their attempted removal, postoperative tetany does not supervene, the absence of acute symptoms is due to the fact that some parathyroid tissue has been left behind, although the most careful search may fail to reveal any.

Accessory Factors in the Results of Parathyroidectomy.—*Effects of Age on the Results of Parathyroid Extirpation.*—As already mentioned incidentally, one factor which appears to influence the effects of parathyroid extirpation is the age of the animal employed. Raynard stated as early as 1834 that this is so in dogs. Horsley (*b*) in 1886 called attention to the influence of age on the results following what he at that time believed to be simple thyroidectomy, but what was in reality in the carnivora thyroparathyroidectomy. He says: "I find that the determining factor, par excellence, of the value of the gland as regards its influence on the general metabolic processes of the animal is age. The effect of removing the gland in the young animal is the rapid appearance of violent nervous symptoms and death in a few days; in a rather older animal, e.g., a one year old dog, the symptoms are less violent, later in their appearance, and the animal survives perhaps for a fortnight or three weeks; in a very old animal the removal of the gland simply hastens the torpor of old age; these observations refer to cats and dogs."

Ewald also observed that the symptoms in aged dogs were usually slight.

MacCallum, Thomson, and Murphy (1907) performed thyroparathyroidectomy in eight goats and five sheep. The sheep were adults and practically no effect was produced on them, and in the goats the most definite results were obtained in the very young. "We do not know how to explain satisfactorily the negative results in so many of these animals, unless it be that, in spite of our extremely careful and conscientious search," both before and after death, "there are still other masses of parathyroid tissue hidden away somewhere in the neck or thorax. It does not seem reasonable to suppose that organs, which are so clearly shown to have a special function in carnivorous and most other animals, should be highly developed in the herbivora and still have no special functional importance." This shows

how preconceived ideas may influence the logic of experienced scientific investigators.

Rossi (1911) in sheep and goats finds, like the last observers, that total parathyroidectomy is often very well tolerated in these animals, while in some cases it leads to tetany, convulsions, and death. He does not give the body weights, and draws no distinction between adults and young animals regarding the severity of the effects. He also believes that failure to produce acute symptoms is due to the presence of accessory parathyroid tissue unintentionally left behind at the operation, although he did not find any such on the most careful postmortem examination.

Berkeley and Beebe (*a*) state that in dogs, after total parathyroid extirpation, the symptoms are more severe in young than in old animals.

Marine, as the result of his own observations, believes that the young are more susceptible than the old. He ligated the superior thyroid arteries in four puppies of the same age (sixty-two days) and litter, and in all tetany developed on the following day, eighteen hours after the ligations. All died a few days later. The inferior thyroid artery, which is normally very small in the dog, was intact and uninjured. In twelve similar operations in adult dogs, none developed tetany. This was, of course, not equivalent to complete thyroparathyroidectomy, but the operation was identical in the two cases.

Simpson found that in sheep age has a profound influence. Four lambs, after the complete operation, showed acute tetany, which ended fatally, while in adult sheep the same treatment led to no visible effects within the three or four months they were kept alive.

Effects of Diet, Pregnancy and Other Factors on Parathyroid Tetany. —Paton and Findlay (*b*) discuss certain factors which may modify the rapidity of onset and the character of the symptoms, viz., diet, age, rickets, pregnancy, and lactation. They confirm, in their own experiments, a statement made by many previous observers, viz., that feeding with meat has a marked effect in increasing the severity of the symptoms, and they frequently employed this method to induce the onset when the condition was latent. They failed to observe any evidence on the effect of age in the dog, but they noted that in very young animals the tonic were more pronounced than the clonic muscular contractions.

They found that rickets appeared to have some influence. They did the complete operation on five puppies about seventy days old with active rickets; in three of them symptoms appeared within twelve hours and in the other two within twenty-four. In puppies of about six months, with healed rickets, the symptoms did not supervene any sooner and were no more acute than in non-rachitic dogs. It would, therefore, appear that active rickets does have an accelerating and accentuating effect on the conditions brought about by parathyroidectomy. In this Paton and Findlay support the previous work of Marine and others.

They had no opportunity of studying in their own experiments the effect of pregnancy and lactation on the postoperative symptoms, but point out that many observers have noted that these conditions appear to augment the symptoms of parathyroid tetany. Carlson (*c*) (1913) found that late pregnancy in dogs accelerates and intensifies the tetanic disturbances in the majority of cases, but that in cats it does not appear to have any influence.

Massalgia (1916) removed three parathyroids from each of two female pups and found that this did not interfere with their development. When they became pregnant, however, both developed tetany. This the author compares with eclampsia, and suggests parathyroid extract as a therapeutic remedy.

Thompson and Leighton showed that trophic disturbances may arise, without acute symptoms, from an incomplete loss of parathyroid tissue, and this has been frequently confirmed. They gradually destroyed the glands by ligation in twenty dogs, and in many observed only chronic trophic changes, without serious damage to the thyroid.

Symptoms of Tetania Parathyreopriva.—Considering the relationship believed by many to exist between the parathyroid glands and idiopathic tetany in the human subject, it is important to become familiar with the clinical picture exhibited by animals following parathyroid extirpation. The symptoms differ in different animals, and in the same animal at different times. They are most severe in dogs and foxes. They have been described by many observers, Schiff, Horsley, MacCallum, Paton and Findlay, and others, some emphasizing one feature, some another, according as these happened to be exhibited more or less prominently in their respective subjects.

Based upon observations on twenty dogs, MacCallum gives a good description of their behavior after complete extirpation of the parathyroids. Usually the animal has recovered perfectly from the anesthetic the next day. If watched carefully, it is seen to begin to show signs of restlessness and anxiety. When one places the hand on the muscles of the head or shoulder, one feels feeble fibrillary tremors; these become more distinct, so that they are evident to the naked eye, and the animal may pass rapidly into a condition in which all the muscles are in rigid spasm; but as a rule the tremors are accompanied by clonic, chorea-like movements of the whole limbs or segments of the limbs, and at this stage, if the animal be laid on its side and a suitable lever attached to either the fore or hind leg, a characteristic tracing, showing the clonic and tonic contractions, may be obtained (Fig. 3).

The dog is able to walk at first, but somewhat stiffly and awkwardly; then he may suddenly fall to the floor, or he may show a staggering, cerebellar gait, superimposed on the dancing movements of his limbs. "Sometimes, in walking about or climbing stairs, the dog suddenly

falls to the floor in an epileptiform convulsion; the legs are stretched out rigid, the head stretched forward, all the muscles of the neck being thrown into tetanic contraction, breathing stops for a few moments and is then gradually resumed, the legs finally relax, and the dog recovers and walks about again."

As a rule, however, the onset of tetany is more gradual and continuously progressive, so that, from the condition in which spastic walking is

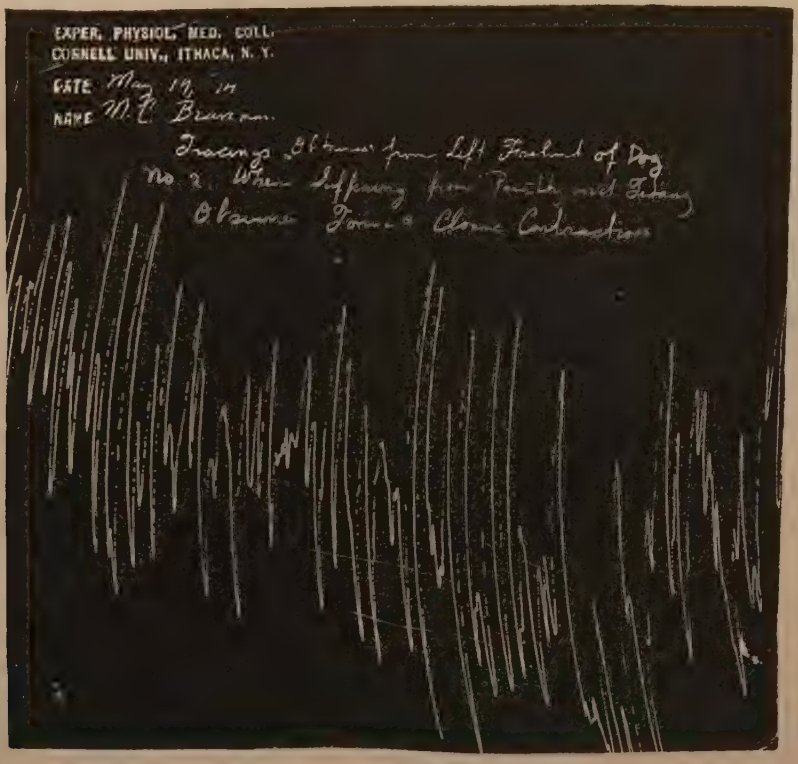


Fig. 3. Tracing from forelimb of a dog in postoperative tetany two days after complete thyroparathyroidectomy.

possible, the dog goes onto the stage in which, with all the muscles rigid and twitching violently, he is unable to stand at all. Frequently there is marked snapping of the jaws, and, as the tongue usually protrudes, it may be badly bitten.

Saliva flows copiously from the mouth, and one symptom which I have frequently observed and have never seen mentioned elsewhere is an apparent itchiness of the mouth and lips; the dog will rub his lips and gums along the wall or in a heap of cinders, if there are any available.

If the attack is a bad one, the breathing is rapid and panting; it may be at the rate of 250 per minute. Whether this is due to excessive muscu-

lar action, or a result of the parathyroidectomy as such, it is difficult to say. I do not recollect to have seen marked acceleration of respiration in the absence of muscular twitching.

The rectal temperature is raised during the fit—I have seen it 109° F. in a dog and about 111° F. in a lamb—and this may also be the result of the intensified muscular activity.

Exhaustion may supervene after a greater or less duration, the convulsions become less violent, respirations reduced, and the dog may remain quiet some time before death; or it may succumb at the height of the seizure, sometimes probably as the result of hyperpyrexia. Not infrequently the animal will recover from one of these acute attacks and remain apparently well for a few hours, or it may be a day or more, until the next attack.

One of the chief characteristics of the condition is its variability from time to time. The animal may be well, to all outward appearance, and in less than half an hour it may be at the height of one of these acute attacks, which may end fatally, or from which it may make a temporary recovery. As pointed out by Paton and Findlay, this extraordinary variability in the severity of the symptoms makes the estimation of the value of curative agents very difficult and uncertain. Even in the middle of a violent attack, if the animal be fully anesthetized, the symptoms disappear, and, when it recovers consciousness, it may seem to be perfectly well. If, during anesthesia, a drug had been administered, or any operative procedure adopted, to this might be attributed curative or ameliorative qualities, and possibly quite erroneously.

In addition to the cardinal features described above, Paton and Findlay (*b*) (1916), from their extensive research, give some further points of interest. The symptoms show less marked variations and are generally less acute in cats than in dogs. In the monkey they are usually slighter still and more chronic, unless in exceptional cases. These observers say that the most marked and constant change in the animal, and this is especially true of the cat, is an alteration in its disposition. It invariably becomes depressed and sluggish, tends to sit drawn up in a corner, and is not easily induced to move. In dogs this depression is, as a rule, much less marked, and between fits it may be almost entirely absent. In the monkey this symptom varies, and its onset may be long delayed, but when the other symptoms manifest themselves it is always present in some degree. Emaciation is another constant feature; the animal generally refuses food and loses weight until death. However, I have seen dogs eat heartily between attacks and drink copiously immediately after one. "These two symptoms, along with the increased excitability of the peripheral nerves, may be considered as the invariable results of the removal of sufficient parathyroid tissue, and they alone may be present up till the time of death."

Stiffness of the limbs, of the nature of an extensor spasm, is often present early, and is increased with voluntary movements. In cats it is rarely severe. This muscular stiffness may be manifested by straddling the hind legs in walking. Paton and Findlay corroborate Morel in the statement that in young dogs this extensor spasm is the prominent motor symptom, and that it may be unaccompanied by any trace of tremors or jerkings. This condition, in the absence of muscular twitchings, "more closely approaches the carpopedal spasm of clinical tetany than does any other stage of tetania parathyreopriva."

Fig. 4. Hand of monkey, dead after thyroparathyroidectomy, from radial and from ulnar sides. (Noël Paton and Findlay.)

While extensor spasm is most common in dogs and cats, in monkeys flexion of the hand and wrist, with adduction of the thumb, may be present; this is the position sometimes taken by the hand in cases of idiopathic tetany in man (Fig. 4).

This stiffness of the muscles, often associated with muscular tremors, appears very early in the cat. It gives rise to movements of the foot, such as are made by the normal animal in attempting to shake water off its pads. This "water shaking" or "paw shaking" is one of the most characteristic features in the cat and is nearly always observed at some stage of the condition, frequently appearing when voluntary movements are made. The muscular tremors in the cat are sometimes marked by the extensor spasms.

The coarse, chorea-like muscular jerkings are usually more prominent

in the dog than in either the cat or monkey. In the dog the respiratory muscles are often involved in these spasms, and artificial respiration is sometimes necessary to restore breathing. Frequently the animal dies in a fit of this kind.

In some cases in the dog paresis appears as one of the earliest symptoms; the animal is unable to stand and may lie prone on its belly with the legs spread and no sign of spasticity. This, however, is not common.

The condition of the reflexes is not characteristic; sometimes they are exaggerated, but often they are less easily elicited than normally; most frequently they are normal.

Sometimes the animal shows muscular disturbances resembling those

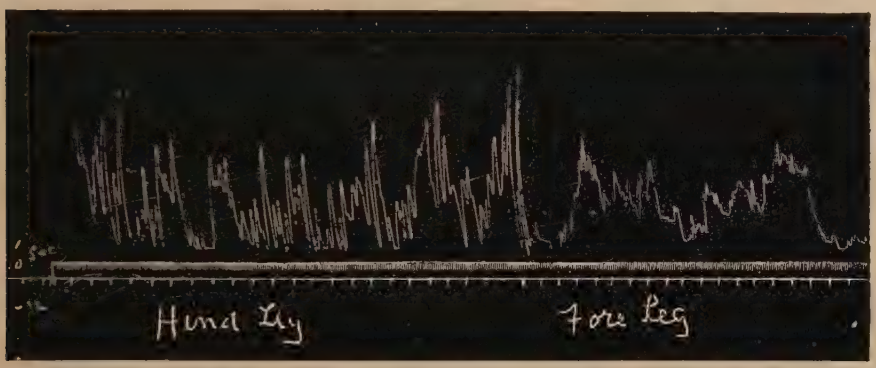


Fig. 5. Record of tremors in hind- and fore-leg of dog, with complete section of the spinal cord. Time in 0.1 sec. and in secs. (Noël Paton, Findlay, and Watson.)

produced by a lesion of the cerebellum. This is more common in the cat than the dog.

Hyperpnea, which is common in the dog, is seldom seen in the cat.

In the dog tachycardia is often present, but this is not marked in the cat.

Intestinal disturbances of a catarrhal nature are not uncommon in the cat.

A semiclosed condition of the eyelids, the opposite of that found in exophthalmic goiter, described by Edmunds as a characteristic symptom, is frequently seen in the cat.

In monkeys, in which the postoperative condition is generally more chronic than in cats or dogs, the course of the symptoms closely resembles that of idiopathic tetany in the human subject, particularly in children.

Relation of the Nervous System to Parathyroid Tetany.—The regions of the nervous system involved in the condition of parathyroid tetany were investigated by Paton, Findlay, and Watson (*b*) (1916). They found that the disturbance proceeds from the central nervous system, since division of the motor fibers to any of the muscles will abolish it. Removal of

the cerebrum increases the violence of the muscular symptoms. These must, therefore, be due to action on the lower neurons. Following transsection of the spinal cord, in the dog, at the level of the first lumbar vertebra, and at the same time thyroparathyroidectomy, it was found that, while the tremors and jerkings persist in the muscles supplied by nerves from the division of the cord which is below the section, but is cut off from the influence of the cerebrum and cerebellum, the sustained tonus in these

Fig. 6. Simultaneous record of the tremors in the fore- and hind-leg of a dog, with complete section of the spinal cord, to show independence of the rhythms. Time in 0.1 sec. (Noël Paton, Findlay, and Watson.)

muscles is abolished. This is shown in Fig. 5 which represents tracings taken simultaneously from fore and hind limbs. It was also found that movements of the hind limbs, after cord section, were entirely independent of the condition of the fore part of the body (Fig. 6). These investigators believed that the tremors and jerkings are due to the condition of the spinal cord and not dependent on the cerebrum or cerebellum, and are caused by an action on the efferent, rather than the afferent neuron in the reflex arc. The integrity of the cerebellar arc is essential for the sustained finer spastic movements. In advanced cases both the cerebrum and cerebellum may be involved secondarily.

The electrical excitability of the peripheral nerves is also increased, and this is one of the earliest signs observable and one of the most delicate indications of diminished parathyroid function. The phrenic nerve may be so sensitive as to be excited by the action currents of the heart, so that the diaphragm twitches with each heart beat. Nevertheless, neither in parathyroid nor in idiopathic tetany is the severity of the symptoms directly proportional to the increased peripheral electrical excitability; hence the latter does not indicate accurately the gravity of the condition.

Hoskins and Wheelon in 1914 noted that after parathyroid extirpation there is demonstrable a marked increase in the irritability of the sympathetic nervous system. Their method was to determine the vasomotor reaction of a given animal to nicotin, which is a selective sympathetic stimulant, and then to remove the parathyroids and, after the development of tetanic symptoms, again to determine the reaction. By this means it was found that the nerve cells proper were affected. Similarly, the use of epinephrin showed increased irritability of the myoneural junctions. An augmented reaction to pituitrin was also interpreted as showing a similar effect in the musculature proper.

Changes in the central nervous system have been described in parathyroid tetany in the direction of cell chromatolysis. Edmunds says they are similar to those observed after acute poisoning.

Degenerative changes in the liver cells have been described by Gozzi and others, but these probably result from the general effects on the organism as a whole which follow the loss of the parathyroid glands, rather than from any direct action.

Experimental Attempts to Augment or Allay Parathyroid Tetany.—The second method of investigation previously mentioned has yielded little positive information regarding the functions of the parathyroid glands. It is recognized that grafting is frequently curative in cases of postoperative tetany. Börcher (1919) says that a single large parathyroid is adequate to obviate symptoms in the human subject. The operation on both donor and recipient may be done under local anesthesia, and the best situation for the graft is in one of the abdominal muscles.

It is reported by many that tetany is relieved by the injection of the extract, or by administration of the gland, fresh or desiccated, by mouth. Assuming that the parathyroid produces an internal secretion, MacCallum and Voegtlin attempted to obtain evidence of this and, if possible, to isolate the active substance. The beneficial effects of transplanting parathyroids and of the injection of parathyroid extracts into animals in tetany have been reported frequently. Berkeley was successful in relieving the symptoms of gastric tetany in a man thirty-nine years of age by the administration of fresh ox parathyroid ground up with milk sugar and given by mouth, and a similar preparation was effective in a case of surgical tetany in man, reported by Putnam.

Berkeley and Beebe (*a*) prepared an extract from beef parathyroids from which they succeeded in separating a nucleoprotein that appeared to them to have curative properties when administered to animals suffering from parathyroidectomy.

This active nucleoprotein was administered to thirty-two animals with typical symptoms of tetany, and it was effective in ninety-five per cent of these. Incidentally, it may be mentioned, that they found no iodin in the analysis of any of the parathyroids examined by them, human, dog, or ox.

Other investigators have been unable to find curative properties in parathyroid preparations. Edmunds fed large quantities to an animal in tetany without any result. On the other hand, Stenvers (1917) describes a case in man with violent tetany (accidental thyroparathyroidectomy), in which the administration of fresh horse parathyroid kept the patient normal until three parathyroids obtained in a goiter operation were implanted. The man was restored to perfect health.

The physiological effects of the intravenous injection of the extract have not been extensively investigated. It is reported to give a fall in blood pressure, as do the extracts of most animal tissues, but no specific action can be assigned to it, despite the fact that such action has frequently been claimed.

The Relation of the Parathyroid Glands to Metabolism.—*Exciting Cause of Symptoms.*—With regard to the origin of the symptoms, already described, which usually appear within a comparatively short time after the parathyroids have been removed, little is definitely known. Two main hypotheses have been advanced by physiologists to explain the effects. These may be designated the calcium deficiency theory and the toxin theory.

Relation of the Parathyroids to Calcium Metabolism.—The view that the nervous and muscular disturbances which follow parathyroid extirpation are due to a deficiency of calcium in the nervous system has been advocated mainly by MacCallum and his pupils, who have brought forward a considerable amount of evidence in its favor.

Studies on Calcium Pharmacology.—In a paper published by MacCallum and Voegtlin in 1909 the literature is reviewed up to that date and the results of their own contributions to the subject recorded. Gregor in 1900 first suggested that the diet might have something to do with the nervous and muscular symptoms in infantile tetany. In the following year Sabbatani, as the result of animal experimentation, stated that calcium salts are antagonistic in their action to sodium citrate. The excitability of the motor cortex is diminished, both to mechanical and electrical stimulation, by the direct application to it of isotonic solutions of calcium chloride. The action is very rapid; immediately after its application a much stronger stimulus is required to produce muscular contrac-

tion. Sodium citrate, sodium oxalate (which precipitates calcium), and sodium soap, have the opposite effect and greatly increase the excitability of the cortex, so that the strength of stimulus needed to produce muscular movements is much reduced. Any substance which precipitates calcium has the same effect and, in sufficient concentration, may lead to spontaneous muscular twitchings and epileptiform seizures. One may apply sodium citrate to the motor area of one hemisphere and calcium chloride to that of the other, with the result that the excitability on one side is markedly increased and on the other side diminished. Considering this soothing influence of soluble salts of calcium, Sabbatani suggests it as a remedy in epileptiform seizures.

Howell studied the effects of depriving excised muscles of calcium and exposing them to the action of calcium-free solutions, such as pure sodium chloride. He noted that rhythmical contractions occur, which may become tetanic, and that these can be checked by the addition of calcium.

Jacques Loeb found that the injection into animals of any salt which will precipitate calcium and so diminish the amount of that substance in solution in the tissues and fluids of the body, produces muscular twitching. Abnormal conditions of metabolism might arise, such as the increase of acid substances, which would thus reduce the quantity of calcium salts and so lead to muscular disturbances, and he suggests the administration of calcium in the treatment of such cases. He placed a frog's nerve-muscle preparation in solutions of salts which either precipitate the calcium, or render it inactive in some other way, and was able to show records of muscular twitchings. These were immediately suppressed by the addition of fresh calcium, or the transference of the preparation to a solution of calcium of the requisite concentration.

J. B. MacCallum pointed out that salts which are antagonistic to calcium have the power of increasing the peristaltic activity of the intestine and increasing the secretory activity of certain organs, whereas soluble salts of calcium have the opposite effect.

Roncoroni showed that the reduction of calcium in the blood circulating to the brain produced the same effect as was obtained by Sabbatani; the excitability of the motor cortex was greatly increased, provoking epileptiform phenomena, which were quickly suppressed by the addition of the requisite amount of calcium to the circulating fluid. Roncoroni also examined the cerebral cortex, treated with various salts by Sabbatani's method, and found no histological changes which were characteristic.

Dietary Studies on Calcium Deficiency and Tetany.—Thiemich (*b*) pointed out that tetany occurs most frequently in infants artificially fed on cow's milk, and that it probably has something to do with calcium deficiency, which may be associated with digestive disturbances. Japha

also believed that cow's milk is the cause of tetany in bottle-fed infants, and found that, when this was stopped and mother's milk or farinaceous foods substituted, a cure was effected. He also attributed the condition to metabolic disturbances.

Stöltzner (*b*) attempted to find the constituent of cow's milk which was responsible for tetany. His conclusion, after much experimental work, was that calcium is retained in the tissues in excessive amount, due to the fact that the associated intestinal disturbance prevented its excretion in sufficient quantity. He would assign as the cause of tetany excessive retention of calcium or calcium stasis.

Finkelstein (*b*) also found that cow's milk is more favorable for the development of tetany than human, and since the whey, rather than the curd, appeared to contain the disturbing material, he concluded it is due to the salts which are much more abundant in cow's milk.

In relation to the fact, well known to clinicians, that tetany seldom occurs while children are at the breast, it is interesting to note that Morel (*c*), in his experimental work, reported that young parathyroidectomized kittens showed no symptoms while suckling, but suffered from acute tetany when weaned.

Influenced by the work of Sabbatani, Quest analyzed the nervous system in four cases of fatal tetany in children, and found much less calcium than in the normal brain. He concluded that the nervous disturbances are caused by a depletion of calcium, rather than by its increase, as advocated by Stöltzner. He also found that in the fetus and new-born infant the calcium content of the brain is high, while cortical excitability is low. As age advances, the one diminishes (calcium) and the other increases. He also fed dogs on a calcium-free diet and found that the electrical excitability of these animals was greatly increased.

Weigert studied two puppies of the same litter. One of them showed symptoms of tetany when fed on cow's milk, and he found that the calcium content of this animal's brain was much below that of the normal.

Cybulski, studying gastric tetany in children, found a low calcium retention in the convulsive stage, which was increased during convalescence and in normal health. He believed that the symptoms are due to calcium deficiency in the nervous system. Silvestri (*a*) held the same opinion.

Netter (*a*), in three cases of tetany, noted improvement following the administration of calcium salts by mouth.

Von Pirquet (*c*) and Bogen opposed the teaching of Stöltzner that tetany is due to the excess of calcium in the system. Both found the opposite to be the case, viz., that the administration of calcium reduces the excitability of the nervous system.

In postoperative tetany, as already mentioned, many investigators

have asserted that animals fed on an exclusively milk diet show the symptoms less violently than those fed mainly or entirely on meat.

The changes in the teeth of rats first described by Erdheim (*b*), already alluded to, also bear on this point, as indicating some profound alteration in the character of the calcium metabolism of the body caused by the loss of the parathyroids. Erdheim (*c*) noted also that callus formation was retarded on account of the deficient deposition of calcium salts.

Calcium Medication in Tetany.—MacCallum and Voegtlin carried out their experiments on dogs, inducing tetany by extirpation of thyroids and parathyroids. They found that the injection of a solution of a salt of calcium into the circulation of an animal in tetany promptly checks all the symptoms and restores the animal to an apparently normal condition. Tetany may be regarded as an expression of the hyperexcitability of the nerve cells, due to the withdrawal of calcium from them. The effect of subcutaneous injection of calcium, or of giving it by the mouth, is the same as that of intravenous injection, but it appears more slowly.

These observers, during the course of their animal experimentation, were given the opportunity of applying this treatment to a case of postoperative tetany in the human subject. In this case calcium lactate was administered in frequent and quite large doses, with the result that the tetany disappeared in the course of a single day. When the calcium medication was withheld for two or three days, the symptoms of tetany reappeared, only to disappear on the administration of calcium. They also found that the injection of magnesium salts will suppress the symptoms of tetany, although its effects are somewhat confused by the ataxic and anesthetic action of magnesium, as pointed out by Meltzer. The injection of sodium and potassium salts, on the other hand, had no beneficial action, but tended rather to intensify the symptoms.

Calcium Excretion in Tetany.—MacCallum and Voegtlin also studied the metabolism of these animals and found, during tetany, a marked reduction in the calcium content of the tissues, especially of the blood and brain. There was also found to be a greater output of calcium in the urine and feces on the development of tetany, an increased output of nitrogen, and of ammonia in the urine, with a higher ammonia ratio. The ammonia content of the blood was also raised. These investigators drew attention to the remarkable difference between the changes in metabolism respectively after thyroidectomy and parathyroidectomy. There is evidence of some kind of acid intoxication, but its effects are not neutralized by the introduction of alkaline sodium salts. In general, they say, the rôle of calcium salts in connection with tetany may be conceived as follows: "These salts have a moderating influence upon the nerve cells. The parathyroid secretion in some way controls the calcium exchange in the body. It may possibly be that, in the absence of the parathyroid secretion, substances arise which can combine with calcium, abstract it from

the tissues, and cause its excretion, and that the parathyroid secretion prevents the appearance of such bodies. The mechanism of the parathyroid action is not determined, but the result, the impoverishment of the tissue with respect to calcium, and the consequent development of hyperexcitability of the nerve cell, is proven. Only the restoration of calcium to the tissues can prevent this."

In a paper published also in 1909, Berkeley and Beebe (*a*) dispute the conclusions of MacCallum and Voegtlin, and incline toward the belief that the symptoms which follow parathyroidectomy are not caused by any deficiency of calcium in the tissues, but rather by some metabolic toxin, which is ordinarily destroyed or neutralized by the physiological activity of the parathyroids. They found, as MacCallum and Voegtlin had shown, that intravenous injections of a soluble calcium salt will relieve the symptoms almost instantly, even in advanced stages of tetany; it is, they say, one of the most striking results in the range of physiological experimentation. Intramuscular injections were effective after thirty to forty-five minutes, and a similar period is required for the beneficial influence after subcutaneous injection. This effect is, however, only temporary.

The symptoms in the acute stage, according to these observers, point strongly to a poison which acts somewhat like those of the convulsant series, including strychnin, ammonia, and the various xanthin substitution products. Berkeley and Beebe point out that the muscular twitching which takes place when isolated muscle is immersed in calcium-free normal saline solution is of peripheral origin, and can hardly be considered as evidence in a theory to explain an action which is central in origin. In contravention to the claim that a milk diet tends to delay or ameliorate the symptoms on account of its high calcium content, these same investigators declare that some of their animals on a meat diet after operation were given bone ash, so that the calcium intake was much larger than that afforded through a milk diet, and yet these bone ash fed animals had the same tetanic seizures as those fed on meat without bone ash.

In certain pathological conditions, such as diabetic acidosis, there is known to be a large excretion of calcium—sometimes twice the normal—and yet no tetany develops. If this increased excretion of calcium, which may take place over extended periods, can continue without causing tetany, why should a two days' excessive excretion, such as might occur after parathyroidectomy, produce these symptoms, they ask, especially when there is such an abundant store of calcium in the bones of the skeleton to be drawn from?

Another observation, originally made by MacCallum, which Berkeley and Beebe were able to confirm repeatedly, was that, when an animal, in the acute stage of tetany, has approximately one-third of its blood

withdrawn and replaced by normal saline solution, the symptoms are promptly relieved. If the calcium depletion theory were correct, this treatment should make matters worse. Joseph and Meltzer showed that the injection of sodium chloride solution without previous bleeding will allay the neuromuscular symptoms.

In order to ascertain whether calcium were specific in its action, Berkeley and Beebe (*a*) tried strontium and barium salts, as well as calcium. They found that a comparatively large dose of strontium may be given (ten cubic centimeters of a ten per cent solution of strontium chloride to a ten kilogram dog) without any evidence of poisoning. They tried the effect of the injection of strontium salts into ten animals suffering from tetany, and found it scarcely possible to decide whether calcium or strontium gave the better results. The effects of calcium seemed to appear a little earlier than those of strontium, but they are not more complete or lasting. They also tried soluble salts of barium, but, as these have poisonous qualities, they had difficulty in determining the effective and, at the same time, non-lethal dose. Nevertheless, they found it possible to give an intramuscular injection of barium chloride and get fairly prompt relief from the symptoms of tetany. "All four of the metals in this group are effective in relieving the symptoms of tetany. Strontium and calcium salts are comparatively harmless agents and may be given intravenously with perfect safety. Magnesium at one end of the scale is a powerful depressant, while barium at the other is a powerful stimulant; and they are both dangerous to life when given in a dose sufficient to control the symptoms of tetany. Calcium and strontium occupy a comparatively neutral position. It need hardly be said that *barium salts should never be given as a therapeutic measure for the relief of tetany.*"

With the hypothesis before them that the symptoms of tetany are due to the action of some toxin, which, like strychnin, caffein, ammonia, or xanthin, stimulates the central nervous system, they induced muscular spasms by the injection of these substances and then tried the effect of calcium and strontium in subduing them. With strychnin and caffein the results were unsatisfactory, but they showed that the toxic effects of ammonia and xanthin were promptly relieved by both calcium and strontium. They conclude from this series of experiments that the symptoms which follow thyroparathyroidectomy are caused by some toxin produced by the deranged metabolism, and not essentially by any deficiency of calcium, which may itself be due to the starvation cachexia that ensues after the operation. They are inclined to believe that the function of the parathyroids is essentially to produce enzymes, which are of prime importance in the intermediary metabolism of nitrogen.

In 1910 Cooke (*b*), repeating to a large extent the work of MacCallum and Voegtlin, was not able in some respects to confirm their results. His observations with regard to calcium and magnesium excretion extended

over a longer period for each animal than did those of MacCallum and Voegtlin. Taking into account the fact that during tetany, animals frequently refuse to eat, or do not retain food when it is administered to them, he studied first the excretion of calcium and magnesium on a constant diet and during fasting, and second the excretion of the same elements in animals on a constant diet succeeded by a fasting period during which the parathyroids were removed. The animals were catheterized daily at the same hour, and, to obtain constant amounts of urine, 350 cubic centimeters of distilled water was given in the twenty-four hours.

It was found, first, that the brains of dogs dying in postoperative tetany contain a slightly greater amount of calcium than do those of normal dogs, and that the magnesium content is practically the same in normal animals as in dogs in tetany. Second, the calcium and magnesium content of the feces of normal and parathyroidectomized dogs is similar; during fasting the excretion of both salts is diminished. Third, the excretion of magnesium in the urine of dogs on a constant diet, as well as in those fasting, runs parallel with that of calcium, while the excretion of both salts is markedly diminished during fasting. After parathyroidectomy, with the animal fasting, the elimination of magnesium is greatly increased, while that of calcium remains unchanged. The increase in magnesium elimination begins before tetany is observed. Fourth, the increased elimination of magnesium indicates that, although there is a disturbance of inorganic equilibrium, it is not limited to calcium. Cooke suggests that the tetany represents a condition of altered salt equilibrium in the nerve cells, brought about by disturbances in the catalytic processes of the body, which increase the acid factors. His experiments do not support the theory that the symptoms are due to the calcium depletion of the cerebral cortex.

Later Voegtlin and MacCallum (1911) stated, in view of the fact that the symptoms are relieved by transfusion with a calcium-free sodium chloride solution, and that some toxic substance is in all probability present in the blood, the symptoms must be considered as due essentially to calcium deficiency.

Transfusion and Perfusion Experiments in Tetany.—In 1912 MacCallum showed that the galvanic hyperexcitability of the nerves, which is a characteristic feature of tetany, is due to some change in the blood induced by parathyroidectomy. By crossed circulation experiments, i.e., connecting the blood vessels of an animal in tetany with those of the leg of a normal animal, so that this was supplied with tetanic blood, it was demonstrated that an excitability, identical with that found during tetany, appears quickly in the nerves of the normal leg. When the tissues are again supplied with normal blood, the hyperexcitability disappears. Similarly, the flooding of one leg of an animal suffering from tetany with normal blood reduces the excitability of the nerves of that leg to the

normal, while the rest of the animal is in tonic and clonic convulsions. Again, if blood be removed from an animal in tetany, defibrinated and perfused through the vessels of the recently amputated limb of a normal animal, the nerves of this limb will show increased excitability. If normal blood and tetany blood be used alternately in this perfusion experiment, the nerves will become correspondingly normally excitable and hyperexcitable.

In 1913 MacCallum and Vogel tried to determine in what particular the blood is altered during tetany, so that it can produce the hyperexcitability of the motor nerves already mentioned.

Three possibilities presented themselves for consideration. The hyperexcitability might be due to a lack of calcium; there might be produced a toxin which would precipitate calcium in the circulation; or there might be in the body a toxin of the strychnin type with stimulating properties. From their experiments they confess they were unable to decide which of these explanations is the correct one. Parathyroid extract, injected into the circulation of an animal suffering from tetany, relieves the convulsive symptoms, but does not alter the hyperexcitability of the peripheral nerves; its action seems to be on the central nervous system, and not peripheral. Bleeding, followed by transfusion with calcium-free sodium chloride solution, stops tetany and also lowers the excitability of the peripheral nerves. The authors do not admit that this can be ascribed to the removal of a circulating poison, but think it due rather to a general disturbance of the nutrition of the nervous system. When oxalate-like substances are injected slowly into the circulation, the excitability of the nerves is greatly increased. The administration of parathyroid extract does not increase the calcium content of the blood. Their final conclusion is that, "In spite of our efforts to shake it, the theory that tetany is closely dependent upon a disturbance of the calcium content of the blood is supported by stronger evidence than any other idea."

A year later MacCallum, Lambert, and Vogel used another method of investigating the relationship of calcium to tetany and the excitability of the peripheral nerves, suggested by the dialysis experiments of Abel, Rowntree, and Turner. They perfused blood against an artificial fluid, containing practically all the inorganic diffusible constituents of the blood, except calcium, and in this way got rid of a large part of the blood calcium. This dialyzed blood, poor in calcium, when perfused through an isolated extremity, produces an extreme excitability of the nerves quite like that seen in tetany. As a check on this, they used blood containing calcium in the proportion found in the normal blood, diffused against the same artificial solution. This blood, not deprived of its calcium, when perfused through an isolated limb in exactly the same way, caused no hyperexcitability of its nerves. From this they conclude that the hyper-

excitability is due entirely to lack of calcium in the circulating blood. When an attempt was made to replace the blood of the whole animal with this calcium-poor diffused blood, it was not very successful in increasing the excitability, probably because the tissues cannot be sufficiently depleted of their calcium. There is no reason to suppose that the parathyroid secretion, if there be such, is removed by this dialysis; it is probably returned to the body in the perfused blood, so that its absence does not produce the effect. To bring this result into relation with the condition in parathyroid tetany, animals suffering from tetany were bled and the blood was replaced in one case with normal blood, in the other with dialyzed blood poor in calcium. The normal blood was found to relieve tetany at once and to lower the peripheral excitability, while the dialyzed blood did neither. "We, therefore, believe that this is further proof that in the tetany of parathyroidectomy also the twitching and hyperexcitability of the nerves is due to lack of calcium in the blood and tissues."

Uhlenhuth (*b*) tested the action of calcium and magnesium salts on certain thymus fed salamander larvæ showing tetany, and found that both suppressed the muscular convulsions, but failed to prevent the other symptoms of tetany. These, which he believes are due to lesions in the central nervous system, caused by a specific poison produced by the thymus, cannot be influenced by either calcium or magnesium. For the most part, these lesions in the nervous system result in death, in spite of calcium or magnesium administration, which affects only peripheral excitability. Magnesium is more effective than calcium.

Intoxication Theory of Parathyroid Tetany.—*Ammonia as the Toxic Agent.*—As already stated, MacCallum and Voegtlin, in their earlier experiments, found that the ammonia content of the blood of dogs suffering from experimental parathyroid tetany was enormously increased, sometimes reaching a value ten times as high as the normal. There was an increased output of nitrogen and of ammonia in the urine, and increased ammonia ratio also in the urine.

Berkeley and Beebe (*a*) strongly incline to the idea of a metabolic toxin as the cause of the symptoms, since bleeding without other measures gives relief, and they consider, among others, ammonia and xanthin as the possible toxic agents involved. They found that the muscular tremors and contractions produced by both these substances, when given intravenously, were promptly relieved by calcium and strontium. They also observe that in eclampsia and other conditions now believed to be related to parathyroid tetany, large quantities of nitrogen and of ammonia are often found in the urine.

Jacobson (*a*) (1910) injected ammonium salts into the veins of dogs and cats in sufficient quantity to produce symptoms similar to those of tetany. She then estimated the amount, and compared it with that pres-

ent in the blood of dogs and cats suffering from parathyroid tetany and of normal animals, and found that "the concentration of ammonia in the blood of cats and dogs in ammonia tetany is practically equal to that in parathyroid tetany." Her findings thus give support to the view that the increased ammonia in the blood of parathyroidectomized animals is directly responsible for the tetany and the depression symptoms.

Carlson and Jacobson, continuing these studies, found, by using the more delicate method of Nessler in estimating the blood ammonia (Jacobson had employed Folin's method in her previous work), that the ammonia content of the blood of dogs suffering from parathyroid tetany is not appreciably greater than that of normal dogs; and that the intravenous injection of calcium salts, in quantities sufficient to suppress completely the spasmodic symptoms in these animals, does not reduce the concentration of ammonia in the blood. They also noted the fact that calcium salts have a much slighter effect on ammonium tetany than on parathyroid tetany. Other points of distinction are mentioned by them; e.g., dogs suffering from ammonia tetany show a much greater hyperexcitability to auditory stimuli than is found in parathyroid tetany; and again, while transverse section of the spinal cord in the upper thoracic region of an animal showing extreme parathyroid tetany will abolish muscular disturbances below the lesion, in pronounced ammonia tetany it will not do so; the whole body is still involved. They confirm Berkeley and Beebe's statement that calcium and strontium are equally efficient in suppressing the symptoms of parathyroid tetany. From these and other results which they obtained they conclude that ammonia is not the exciting agent in parathyroid tetany. With the exception of parathyroid transplantation, all measures used in the treatment of parathyroid tetany are only palliative, not curative, and act by temporarily diminishing the excitability of the nervous system.

Greenwald (*a*) (1911) found that the excretion of nitrogen was increased only after the onset of tetany, when the muscular action was increased; the proportion of the total nitrogen excreted in the form of ammonia was very little, if at all, increased; the concentration of ammonia in the blood during tetany was not higher than in normal animals. The creatin of the urine was very much increased, while creatinin excretion was only slightly so. There was also an increase of sulphur excreted; and phosphorus was at first retained, but when the symptoms appeared, it was excreted in excess.

Albertoni also failed to find any increase of ammonia in the blood during tetany.

Cooke (*c*) (1911), on the other hand, reports an increase in the nitrogen and ammonia in parathyroidectomy. In some animals lactic acid was found in the urine.

Gertrude Bostock, in Paton's laboratory, found that the muscular

tremors and convulsions produced by the injection of ammonium carbonate persist when the animal is fully anesthetized, whereas the convulsions in parathyroidectomy are suppressed by full anesthesia, as was shown by Paton and Findlay.

Voegtlin and MacCallum noted in incipient parathyroid tetany that the peripheral excitability was increased and that the intravenous injection of ammonium salts had a preventive effect, rather than otherwise.

Wilson, Stearns, and Thurlow consider that deranged metabolism, whereby the normal equilibrium of acids and bases in the blood is disturbed, is the cause of the symptoms of parathyroid tetany. After parathyroidectomy, before any symptoms appear, a condition of alkalosis may develop, but when the active muscular contractions of tetany begin, this alkalosis is obviated by the acid products, so that, after periods of acute tetany, a condition of acidosis may result. Wilson, Stearns, and Janney showed that the increased excretion of ammonia only begins after the muscular action is in evidence, and is produced probably to neutralize the acidosis which results.

Togawa found a condition of acidosis in dogs suffering from parathyroid tetany, and the antitryptic and non-protein nitrogen content of the serum were usually increased. In thyroidectomized dogs, with no tetanic symptoms, acidosis is never observed, but sometimes a slight alkalosis is present.

On the whole, the evidence in favor of ammonia as the exciting agent is unsatisfactory. There are many essential points in which the symptoms of intravenous injection of ammonia differ from those of parathyroidectomy.

Xanthin as the Toxic Agent.—With regard to xanthin, this, in the hands of Berkeley and Beebe (*a*), produced effects which were allayed by calcium and strontium, but Voegtlin and MacCallum failed to confirm the observation.

Histamin as the Toxic Agent.—β-iminazolylethylamin has also been suggested by Biedl, on account of its relation to ergot, but Dale and Laidlaw, who investigated the action of this substance, find that it affects mainly visceral muscle; striated muscles, which are notably involved in parathyroid tetany, hardly at all.

Guanidin and Methylguanidin as the Toxic Agents.—Koch (*a*) (*b*) in 1912 and again in 1913 reported the discovery of methylguanidin in considerable quantity in the urine of parathyroidectomized dogs suffering from tetany. In a series of important papers published in 1917 Paton and his pupils have brought forward many strong arguments in favor of these substances as the toxin or toxins which are the exciting agents in parathyroid tetany. The literature of previous work on the action of guanidin is given in the communication by Paton and Findlay (*c*) (1916) presenting the results of their own contributions to the subject.

They made an extensive series of experiments on the action of guanidin hydrochloride and methylguanidin nitrate on the cat, rat, and rabbit, and in all of these the symptoms produced were indistinguishable from those of the tetany following parathyroidectomy. Fig. 7 shows the tracing taken from a cat after the intramuscular injection of guanidin hydrochloride. The electrical reactions of the peripheral nerves were measured and found to correspond with those obtained in parathyroid tetany.

They tested the action after section of the spinal cord and after spinal section followed by decerebration, and found that the absence of tone in the hind limbs after section of the cord and the persistence of the symptoms after decerebration were similar to the results obtained following the same

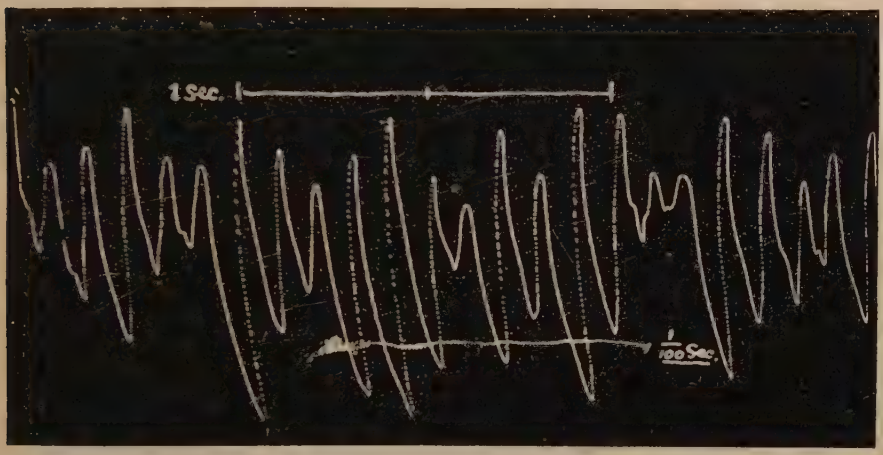


Fig. 7. Tracing of tremors of hind-legs of cat after guanidin. (Noël Paton and Findlay.)

procedures in animals with parathyroid tetany. They injected guanidin into the subdural space and found that in small doses it excites the cord, as in tetany, but in larger doses it has a depressant action. The actions of guanidin and methylguanidin were antagonized by calcium lactate, and it was also shown that latent tetany in the early stages of parathyroidectomy could be transformed into active tetany by the administration of a dose of guanidin insufficient to produce any effect in the normal animal.

The elements acted on peripherally by guanidin, viz., the nerves or nerve endings, are the same as they found to be affected in parathyroid tetany. After parathyroidectomy the electrical excitability of the peripheral nerves is not always proportionate to the severity of the symptoms, and after the administration of guanidin the peripheral nerves may not be influenced at once.

As a matter of fact, the symptoms are rarely so violent in parathyroid tetany as after the injection of guanidin, since probably when developed in the body the concentration is not so great. Another point of interest is the

chronic character of the symptoms produced by a single dose. In one animal (cat) the effect of a single dose lasted from December 23 till January 2,—ten days.

Paton and Findlay conclude that in "all particulars the symptoms produced by the administration of methylguanidin or guanidin are identical with those which manifest themselves in tetania parathyreopriva. The spasticity, the tremors, the jerkings, the disturbances of balance, and the increased electrical excitability of the neuromyon are all present. As in tetany, so in guanidin poisoning, the course and character of the symptoms vary greatly in different animals and at different times." The same part of the nervous system appears to be affected in the two conditions. The symptoms of guanidin injection bear the "same relationship to those of tetania parathyreopriva that those following the administration of diphtheria toxin bear to the symptoms of true diphtheria."

Burns and Sharpe, working in Paton's laboratory, determined the amount of guanidin and methylguanidin in the blood and urine of normal dogs and in dogs from which the parathyroids had been removed; also in the urine of children free from tetany and of others suffering from it. The guanidin or methylguanidin content of the blood of normal animals had never previously been estimated. Small quantities of guanidin and methylguanidin have been found in normal human urine by Kutscher and Lohmann and by England. Feeding on meat extract increased their output, according to Kutscher and Lohmann and to Achelis. The latter obtained these substances also in the urine of the horse.

Burns and Sharpe criticize the methods of previous workers and give their own in detail. The blood of the normal dog (average of five cases) yielded one milligram of guanidin (and methylguanidin expressed as guanidin) per 1000 cubic centimeters, while that of parathyroidectomized dogs (average of eight cases) gave 8.7 milligrams, that is, more than eight times as much. In the normal dog's urine they obtained one-fourth of a milligram (average of six cases) and 1.1 milligram in that of parathyroidectomized dogs (average of 6 cases) per 1000 cubic centimeters. In the urine of normal children the average figure was 0.12 milligram; in children suffering from idiopathic tetany it was, in the active stage 0.58, latent tetany 0.38 and after recovery from tetany 0.12 milligram per 1000 cubic centimeters. From these figures it will be seen that there is a marked increase of these substances in the blood and urine of parathyroidectomized dogs and in the urine of children in idiopathic tetany.

Wishart tested on frog's muscle the action of blood serum obtained from parathyroidectomized dogs and cats in active tetany. It had been found by earlier observers that isotonic solutions of guanidin in Ringer's mixture gave rise to a peculiar twitching in frog's muscles placed in it. This test, if successful, would be additional confirmation of the presence of guanidin in the blood, and could be readily applied. They found that

not all frog's muscle preparations were responsive, and this biological test, on that account, is not entirely reliable. In certain cases, however, the serum acts upon the muscle in the same way as do dilute solutions of guanidin and methylguanidin. An example is seen in Figs. 8 and 9. After seventeen minutes' immersion in the serum of a cat which had been showing marked symptoms of parathyroid tetany for three days, a frog's gastrocnemius gave spontaneous twitchings, recorded in the upper tracing of Fig. 8. This figure shows the gradual development of the spontaneous muscular contractions. Frequently, when a single stimulus was applied to the muscle immersed in the serum, a simple muscle twitch was obtained, but it was markedly prolonged, resembling the complete tetanus of frog's

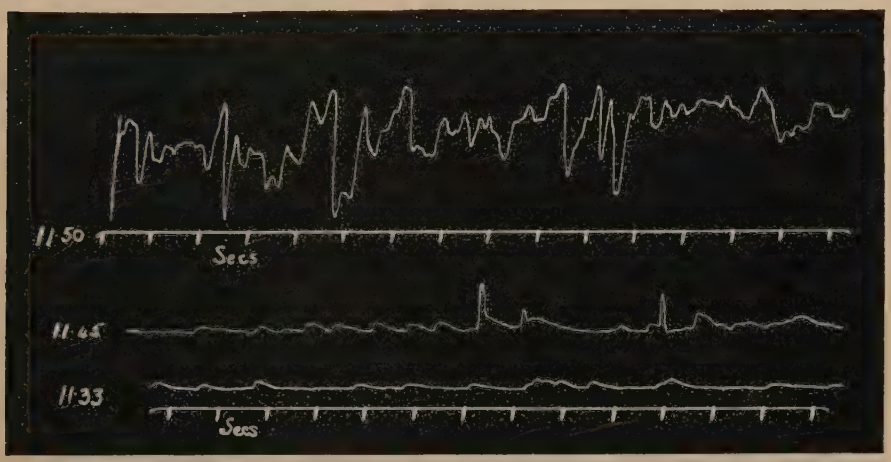


Fig. 8. Showing the gradual development of tremors or spontaneous contraction in the frog's gastrocnemius in serum from the blood of parathyroidectomized cat. Time in secs. (Wishart.)

muscle (Fig. 9). The serum of normal dog's and cat's blood caused no such tremors or prolonged contractions. Burns studied nitrogen elimination in dogs after guanidin administration and after parathyroidectomy, and found that the results showed a marked similarity. Following the administration of guanidin the excretion of nitrogen was increased immediately and out of all proportion to the dose, while the ratio of urea nitrogen to total nitrogen was decreased. The ammonia excretion was slightly decreased in feeding animals and showed a slight increase in animals that refused food. The excretion of creatinin showed only a very slight increase, if any at all, and the percentage of undetermined nitrogen rose markedly immediately after injection of guanidin. In every respect the protein metabolism of parathyroidectomized animals is very similar to the above.

Burns and Watson (*a*) (1920) found that guanidin intoxication and parathyroid tetany, in many respects, have a similar effect on the heart and

circulation. For example, both produce an interference with vagocardiac inhibition, which is removed by salts of calcium.

Watanabe (*e*) (*f*) supports Paton's guanidin theory of parathyroid tetany. By the administration of guanidin hydrochloride to rabbits he was able to produce hypoglycemia, which also occurs after parathyroidectomy.

Koch (*d*) (1918), in an elaborate article, discusses the physiology of the parathyroid glands. He claims to have put forward the guanidin theory in 1913, and agrees with Paton's views. The precursor of guanidin may

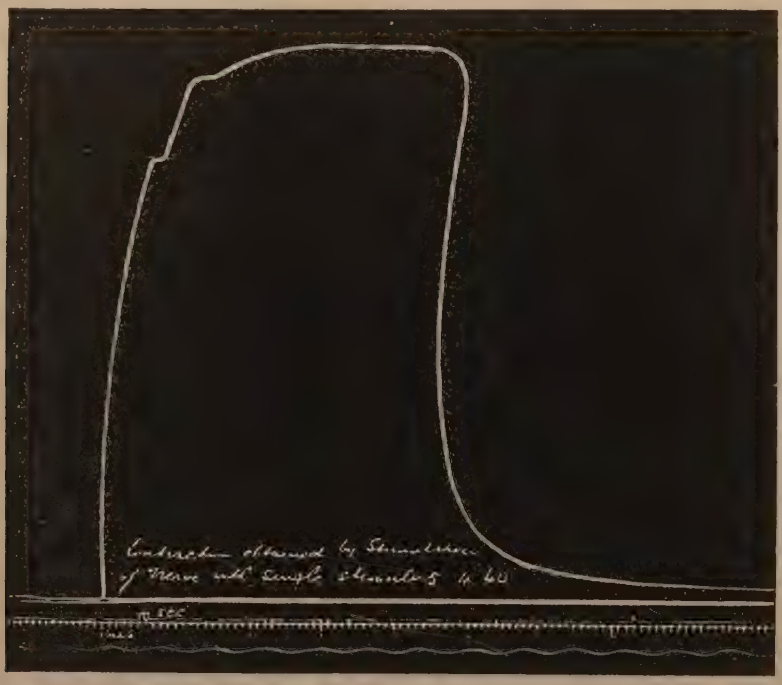


Fig. 9. Tetanus-like response to single stimulus of frog's muscle immersed in serum from blood of parathyroidectomized dog. Time in 1/10 sec. (Wishart.)

be cyanamid. Calcium alleviates tetany because it decreases the permeability of the body cells, which allows them to take up guanidin. In another communication he makes a further contribution to the subject.

Henderson estimated the guanidin in muscle, and found that there was a fall in the total and in the free guanidin after parathyroidectomy, and a rise in creatin. This may indicate either a liberation of guanidin from the muscle, or a failure in the power of the muscle to take it up from the circulation. Either hypothesis will account for the fact that guanidin is increased in the blood.

Sharpe estimated the guanidin in the feces of normal children and those suffering from idiopathic tetany, and found that in the latter it was greatly increased.

Petersen, Jobling, and Eggstein found that a progressive increase in the non-coagulable nitrogen and proteose of the blood follows the operation of thyroparathyroidectomy. The amino-nitrogen is usually increased when tetany is at its height.

Inosinic Acid as the Toxic Agent.—Greenwald (*b*) had previously called attention to a marked retention of phosphorus after parathyroidectomy in dogs, followed by a retention of sodium and potassium. It had been shown that inorganic phosphates cannot give rise to tetany. Other phosphorus compounds were sought as the possible toxic agents, and inosinic acid, one of the simplest of the nucleic acids, was investigated. An intravenous injection of inosinate of soda into a dog recently parathyroidectomized gave rise to no symptoms of tetany; therefore, it was concluded that the toxic agent was not inosinic acid. The significance of the retention of phosphorus remains unexplained.

Thymus Secretion as the Toxic Agent.—Uhlenhuth (*a*) (*b*) (*c*) (*d*) (*e*) (1917) showed that in thymus-fed salamander larvæ tetany supervenes similar to that in parathyroidectomized mammals; when they develop parathyroids (at the time of metamorphosis) the tetany symptoms disappear. The theory is advanced that the thymus produces substances which cause tetany and secretes them into the body, from which they are removed by the parathyroids. Removal of the latter would produce tetany. In subsequent papers he elaborates this theory and presents additional evidence.

Honeyman tested Uhlenhuth's theory that the thymus produces a toxin which causes tetany in the absence of the parathyroid in certain salamander larvæ, when applied to the mammal. He removed the thymus and the parathyroids at the same operation in the guinea pig. This did not modify in any way the onset of symptoms of tetany. In the mammal, then, it appears unlikely that the thymus secretes or contains any substance capable of producing tetany.*

Physiology of Parathyroid Glands

With regard to the functions of the parathyroid gland, it must be admitted that our knowledge is still somewhat obscure. Various ideas have been prevalent from time to time concerning this.

One theory is that the secretions of the thyroid and parathyroid glands have antagonistic actions on the central nervous system. The most obvious effects of the removal of one or the other are the nervous symptoms which follow—in the one case depression, in the other excitation—and it is assumed that the autocoid produced by the parathyroid is a chalone—which according to Schafer may be termed provisionally parathyrin—

* Park has shown that complete thymus extirpation in the guinea pig is not feasible. R. G. H.

whereas that secreted by the thyroid is a hormone, or exciting agent. Normally the two neutralize each other; when one is absent, the other produces its action uncontrolled. This theory was first advocated by Rüdinger. An obvious objection to it is the fact that the nervous excitation which follows removal of the parathyroid is not affected by the subsequent destruction of the thyroid, as it should be, if the two glands were normally antagonistic. The statement of Vassale and Generali that the symptoms of parathyroidectomy are more severe than those of thyroparathyroidectomy has not been generally upheld. Frequently it is found that removal of the parathyroids is followed, from the beginning, by depression instead of overexcitation, not of the same nature but to some extent resembling that of simple thyroidectomy, and this cannot be readily explained on the above theory.

The calcium deficiency theory has been advocated mainly by MacCallum and his collaborators. According to MacCallum, the secretion of the parathyroid glands regulates the metabolism of calcium in the body in some way at present unknown, and when this control is interfered with by the absence of these glands, there is a depletion of calcium in the tissues. This reduction in the calcium content of the central nervous system is the essential cause of the acute neuromuscular disturbances seen in parathyroid tetany; for it has been recognized since the work of Sabbatani that calcium in excess depresses the excitability of the cerebral motor cortex, and that its diminution or absence has the opposite effect. How the calcium content of the tissues is affected by the parathyroid secretion is not clear, but one suggestion by MacCallum is that "it must govern the conversion of a non-dialyzable and ineffective combination of calcium into a dialyzable form, which is essential for the control of the excitability of the nerve."

The main argument in support of this idea is the undoubted fact that the injection of soluble salts of calcium gives immediate relief from the nervous symptoms of parathyroid tetany. This, however, is only palliative and when repeatedly applied may prolong the life of the animal, but does not preserve it. The strongest objection to it is that other elements are as effective as calcium, and particularly, that simply bleeding the animal and then replacing the blood shed by an equal amount of calcium-free isotonic solution of sodium chloride will also bring prompt relief.

The fact that bleeding alone will relieve the symptoms produced by absence of the parathyroids suggests the toxin theory of parathyroid function. This, in its present form, which may be termed the Guanidin Theory, was first suggested by the observation of Koch that methylguanidin is present in the urine of dogs suffering from parathyroid tetany. It is advocated by Noël Paton and his pupils, and is supported by an imposing array of facts brought forward by them. These are presented in an important series of contributions published in the *Quarterly Journal of*

Experimental Physiology, 1917, to which the reader is referred for details. As stated briefly by Paton, "the parathyroids control the metabolism of guanidin in the body by preventing its development in undue amounts." The cause of parathyroid tetany is guanidin intoxication acting on the central nervous system and peripherally on the myoneural junctions. According to Koch, "a mother substance from which guanidin may be formed is cyanamid, a body which may be recovered in methylated form from the urine of parathyroidectomized dogs. The cyanamid can readily take up ammonia to form guanidin. If not so converted to guanidin, it is readily hydrated into urea."

The main facts in favor of the guanidin intoxication theory are, first, that symptoms identical with those of parathyroidectomy may be produced in animals by the injection of soluble salts of guanidin; that guanidin is greatly increased in the blood and urine of animals suffering from parathyroid tetany; that nerve muscle preparations are affected alike by solutions of guanidin and by the serum of animals in parathyroid tetany; and that articles of diet rich in creatin, such as meat, greatly aggravate the symptoms.

One of the circumstances most difficult to explain in experimental parathyroidectomy has been the divergent results obtained by competent operators, using different species of animals. The predecessors of Gley explained this on dietetic grounds, and future investigation may show that the results depend more largely on metabolic changes than the theory of the indispensability of the parathyroids will allow.

Paton also believes that tetania parathyreopriva and idiopathic tetany are due to the same cause, viz., diminution or suppression of parathyroid function. Histological evidence on this point has, however, so far, not been conclusive.

Chemistry of the Parathyroid Glands

Our knowledge of the chemistry of the parathyroids is, as yet, very imperfect. In 1897 Gley (*c*) reported the presence of iodin in these glands in the rabbit and dog in comparatively large quantities. He used the method of Baumann, somewhat modified, and attempted to estimate quantitatively the iodin in the thyroid and parathyroids of each animal separately. He presents his results in tabular form in six rabbits and five dogs, and his conclusion is that in the rabbit the amount of iodin found in the parathyroids is actually greater (about 2.35 times) than that in the thyroid, while relatively it is much greater (about 37 times). In the dog, while the absolute amount found in the parathyroids was less than in the thyroid, relatively it was much higher.

From the fact that, according to his findings, Gley believed that both

glands contained such a high percentage of iodin—much more than any other organ in the body—he concluded that they belong to the same system functionally—the "thyroid system of organs." Subsequent research has not given support to Gley in this matter.

In the literature Mendel is frequently cited as having found more iodin in the parathyroids than in the thyroid in the human subject, both relatively and absolutely, but in this he is misquoted, as his statement refers to accessory thyroids, which are occasionally found, and not to the parathyroids.

Chenu and Morel in 1904 repeated the analyses of Gley in dogs, rabbits, and chickens, using the Baumann method. They separated completely the external parathyroids from all surrounding tissue, dried them on filter paper, and, at the same time, took from the same animal, recently killed, a small portion of the thyroid equal to the combined weights of the external parathyroids. With the colorimeter they were able to detect iodin to 0.0025 milligram, and in the parathyroids of no single animal was it equal to this amount, although in the same weight of thyroid it could be estimated, as a rule. In the chicken, for example, while the iodin in the parathyroids was less than 0.0025 milligram, and its exact quantity could not be determined, in an equal amount of thyroid tissue it was 0.0110 milligram and 0.0140 milligram, respectively, in the two analyses given.

That the parathyroids, like other organs, do contain traces of iodin, if a sufficient quantity of the tissue be secured, they showed by collecting these glands from eight dogs (0.133 gram) for a single analysis. One gram of fresh dog parathyroid they found by calculation would contain 0.0563 milligram of iodin, which for each animal would be only a trace—less than the method was capable of indicating.

Later workers have corroborated Chenu and Morel. Estes and Cecil carried out a similar investigation in dogs, cows, horses, sheep, and man, not taking the glands from a single animal, but collecting a number from several of the same species, in order to obtain a sufficient amount of material for analysis. Baumann's method was employed, choloroform being used instead of carbon disulphid for the colorimetric test, and with this, iodin to the amount of 0.0025 milligram could be detected. In the dog 0.25 gram and 0.24 gram of dried parathyroid—two estimations—yielded only infinitesimal amounts of iodin. In the cow (when as much as 0.5 gram of dried parathyroid was used for a single analysis), horse, sheep, and man the results were always negative, except in one case, in which 3.78 grams of dried horse parathyroid yielded 0.06 milligram of iodin. Two other analyses from the horse gave negative results. Estes and Cecil call attention to the fact that in the dog and other carnivorous animals, in which the two organs are intimately associated anatomically, it is hardly possible to be certain that no thyroid tissue has adhered to the

parathyroids in the process of separation, and this might account for the traces of iodin found in the parathyroids of this animal in their analysis. The same may be said in the case of the human parathyroids. Their conclusion is that, if present at all, iodin occurs in such minute quantities in the parathyroids as to be of no functional significance, and that there are no chemical grounds for the hypothesis that the thyroid and parathyroids belong to the same physiological system.

The work of Berkeley and Beebe along these lines has already been adverted to. In attempts to obtain the active principle of the gland they used a normal saline extract of ox parathyroid. This contained a mixture of nucleoprotein, globulin, and albumin, which they proceeded to separate chemically. They divided the protein content of the extract into three portions, "the first being precipitated by acetic acid, the second by half saturating the filtrate with ammonium sulphate, and the third by complete saturation with ammonium sulphate." Following the common nomenclature, they speak of these proteins as nucleoprotein, globulin, and albumin. The nucleoprotein was by far the most abundant, the yield being five times as great as that of the globulin, while the albumin was present in very small quantity. After purifying the nucleoprotein and globulin, their actions were tested on animals suffering from parathyroid tetany, and from the results the authors believed that the active principle was contained in the nucleoprotein alone. "The nucleoprotein of the parathyroid, when freshly prepared, is equal to the whole gland in relieving the symptoms of acute tetany in dogs," while the globulin had no such effect. Boiling the nucleoprotein, or keeping it at a temperature of 80°C for half an hour was found to destroy its activity completely; it rapidly deteriorated in solution or in suspension at refrigerator temperature, while freezing also destroyed its activity. Tryptic or peptic digestion for forty-eight hours severely impairs, but does not completely destroy its activity. These properties would seem to show that the active principle belongs to the class of enzymes, rather than to that of the autocoids. They state that it relieves tetany when administered by mouth, but it acts more rapidly and effectively when given by subcutaneous or intraperitoneal injection.

The action of the globulin was always negative, and the albumin was not obtained in sufficient quantity to permit of the biological test being applied to it.

Berkeley and Beebe found no evidence of iodin in any of the parathyroids which they examined—human, dog, or ox.

In 1905 Vassale (*c*) prepared an extract from the parathyroids by a "special method," which he does not describe, and found it to be effective when given orally, or by subcutaneous injection in eclampsia, infantile tetany, and epilepsy.

The resemblance of some of the symptoms of parathyroid tetany to

the effects produced when creatin is applied to the motor areas of the cerebral cortex suggested to Rowe the idea that the tetany in a parathyroidectomized animal may be produced by the accumulation of such a nitrogenous substance as creatin, which in normal animals is changed by the parathyroids into a harmless, non-toxic substance, and that this change may be effected by a creatin-splitting ferment contained in that gland. Unable to obtain a sufficient quantity of pure parathyroid material, he was compelled to use the sheep's thyroid, which, like this gland in other species, contains parathyroid tissue, hoping that any pronounced action of the parathyroid would be shown by an increased rate in the breaking down of creatin. He did find evidence of a creatin splitting ferment in the thyroparathyroid tissue, as Gottlieb and Stangassinger had done previously; since, however, the proportion of parathyroid tissue in the composite organ is so small, this is no proof that the enzyme in question belongs to the parathyroid rather than the thyroid.

Guizzetti (*b*) (1911) examined the parathyroids for glycogen. In many animals it was found to be entirely lacking, in others it was present in traces, while in some, e.g., the cat, it was found in relatively large quantities. Glycogen may frequently be detected in the gland cells and also in the interstitial spaces.

Fat is found in considerable quantities in the parathyroids of the adult, and is said to increase with age, although this is not certain. In general, however, it is most abundant in elderly individuals.

Whether it is correct to consider the colloid material which is sometimes found in the parathyroids as a normal constituent of these glands is not clear. It is stated that colloid is found in fourteen per cent of cases in man, and that, for individuals over twenty, a certain amount of it in the parathyroids is not to be considered abnormal. Whether it is a true secretion product of the gland cells or results from degenerative changes is not known, and its identity, chemically and physically, with the colloid of the thyroid has not been established.

Toxic effects in certain individuals, resulting from the prolonged therapeutic administration of parathyroid substance, have been described by Morris and by Berkeley, while Salvioli and Carraro find experimentally that watery extract of ox parathyroid acts as a poison to heart muscle.

Summary

Prior to the time of Gley (1891) operative interference with the thyroids led to conflicting results, since the existence of the parathyroids was unknown. Subsequent to the rediscovery of the external parathyroids by Gley the acute symptoms were held to be due to the loss of the parathyroids and the chronic cachexia to that of the thyroids; but the former were be-

lieved to be embryonic thyroids capable of developing into functionally active tissue, so that really all the effects were due to the loss of the thyroids.

After the discovery of the internal parathyroids by Kohn, the embryonic character of the parathyroids was rejected by most, but still advocated by a few, and it was taught that they were separate and independent organs, functionally and embryologically, and had only an anatomical relationship to the thyroid. In thyroparathyroidectomy their absence was alone responsible for the acute neuromuscular symptoms. Failure to obtain these in any experimental animal was ascribed to their incomplete removal, or to the presence of accessory parathyroids inadvertently left behind.

Functionally, the parathyroid glands were believed to regulate calcium metabolism; interference with this led to a depletion of calcium in the tissues and, as a consequence, to hyperexcitability of the nervous system.

Failure of this theory to account for many experimentally determined facts led to its abandonment by most, in favor of the Guanidin Intoxication Theory, which by many is at present held to explain the symptoms of parathyroidectomy in animals and idiopathic tetany in the human subject. Both conditions are believed to be practically identical and to be due to absence or depression of the parathyroid function.

In the preparation of this article, in addition to the references specifically given, the following monographs have been consulted: "The Endocrine Organs," by Sir Edward S. Schafer, London, 1916; "Internal Secretion and the Ductless Glands," by Swale Vincent, London, 1912; "Surgery and Pathology of the Thyroid and Parathyroid Glands," by Ochsner and Thompson, St. Louis, 1915; and "Innere Sekretion," by A. Biedl, Wien, 1916. The last three contain bibliographies, very complete up to the dates of their respective publications.

Pathological Anatomy and Histology . . . . . *Oskar Klotz*

Introduction—Anomalies—Inflammatory and Fibrotic Reactions—Degenerations—Hemorrhage into the Parathyroids—Tumors.

3. Pathological Anatomy and Histology

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Introduction

Paucity of Data.—Partly on account of the small size, the hidden position and the difficulty in recognizing the parathyroid glands in the gross specimen, routine examination of them is not undertaken at the autopsy table, and hence reliable statistics on the incidence of various disease processes within these glandules are not available. Furthermore, as an accurate knowledge of the relationship, save in a few conditions, of these tiny structures to clinical manifestations is not clearly known, the general pathologist has not been sufficiently impressed with their importance to spend the necessary time in a study of their gross and microscopical characters. When the parathyroids are analyzed, sufficient information to be of value cannot be gained by a naked-eye examination alone, but must be followed up by a careful microscopical study of each glandule which is isolated. It is, therefore, impossible to lay much stress on the sporadic reports of the occurrence of lesions within the parathyroids and their bearing upon symptoms during life.

Neglect of the Study of the Parathyroids.—The lesions which have been reported in the parathyroids have, in large part, been described by those who set themselves the special task of analyzing them in a limited number of cases. In a certain number of instances attention was attracted to the parathyroids by the presence of tetany, altered calcium metabolism, imperfect development of bones and teeth, as well as nutritional disturbances in infants, in which it has been shown through animal experimentation that the parathyroids may have been primarily at fault, or have suffered associated disturbance. I know of no laboratory in which the parathyroids receive routine attention at the autopsy. It is probable that tissue changes are more frequent within the parathyroids than is indicated by the various reports; and it is also probable that the parathyroids suffer damage in diseases which affect the body at large, and that such disturbances may assist at times in inducing new complexities in the clinical manifestations.

Participation by the Parathyroids in General Reactions to Disease.—It is well known that during severe infections and intoxications, not a few tissues are injured in a secondary process, and often without significance to the clinical symptoms which have been present. We are reminded of the not uncommon presence of petechial hemorrhages in many tissues and organs occurring as a late event in infections. Furthermore, an appreciation of the correlation of functional activities, particularly as have been suggested for the organs of internal secretion, must be more thoroughly obtained before we shall be able to interpret the deficiency or exaggeration of function occurring in as minute structures as the parathyroid glandules, when morphological change may be absent, or so slight as to escape our attention. Whether the parenchyma of the parathyroids suffer fatigue or exhaustion of function to a degree which will manifest symptoms, but where the tissue elements have not suffered structural change, has as yet not been clearly defined. That such may occur has been suggested by many, but in the absence of a method whereby the active principle of the parathyroid may be recognized in its physiologic and pathologic quantity, such derangement can be suggested only in a tentative manner.

Infrequency of Definite Parathyroid Lesions.—Degenerative processes have been shown to arise where the body suffers from an inflammatory intoxication, and in a few instances true inflammatory reactions localizing in these structures have been described. It is unusual, however, that an inflammation resulting from bacterial localization, as observed in many other tissues, takes place in these glands. It is less frequent than that observed in the thyroid, and it is infrequent to note an inflammatory process developing from contiguous structures. Broadly speaking, although the parathyroids may suffer the various lesions, as seen in other tissues, their actual presence is infrequent and localized to one or other of the glands, permitting the remaining number to adequately carry out the function belonging to these structures.

Inconstancy of Parathyroid Lesions in Diseases.—In not a few diseases where analogy with the results of animal experimentation suggests involvement of the parathyroids, the surmise has not always been verified by postmortem analysis. In the lack of knowledge of the active secretion of the parathyroid, and our ignorance of what constitutes a condition of hypoparathyroidism, we are unable to give an adequate interpretation of the disease manifestations in the presence of glandules which to the eye possess a normal structure. In these analyses we are again brought face to face with the fact that a morphological study gives little clue as to the functional capacity of a given tissue. It is necessary that more data be assembled in order to give proper place to the lesions of the parathyroid and their relation to conditions other than tetany. The progressive alterations of these tissues with advancing age, and the changes concomitant with

acute infections and intoxications must be thoroughly understood to appreciate their rôle in health and disease.

Margin of Safety in Parathyroid Deficiency.—It has been amply illustrated in the experimental work that the sudden and complete deprival of the parathyroid tissues in animals leads to the development of marked symptoms with convulsions and death (tetany). Such destruction of the parathyroid may be accomplished by excision, or by the crushing of tissues accompanied by hemorrhage. It has been estimated that at least three-quarters or more of the functioning parathyroid tissue must be destroyed to bring about these severe manifestations (Thompson and Leighton), and it is probable that the same quantitative conditions hold for the spontaneous development of the manifestations of parathyroid deficiency. It must be recognized, however, that it is likewise possible to have minor lesions occupy one or more of the parathyroid glandules, without having our attention attracted to the injury in the absence of specific symptoms. This has been observed in cases where tumor has occupied one or more of the parathyroids (Thompson (*c*), Koenigstein), in which during life no evidence of functional insufficiency has made its appearance. Similar observations have been made in cases where hemorrhage has occurred into the parathyroids, but has not completely destroyed their activity (Thiemich (*c*), Haberfeld).

Manifestations of Slowly Developed Parathyroid Deficiency.—Thompson and Leighton have shown that when the parathyroid function has been slowly disturbed the manifestations are not those of acute tetany, but more of the nature of nutritional disturbances with trophic change. Erdheim has commented upon the peculiar functional disturbances associated with enamel defects, fracture of teeth, and occasional gastrostomatitis, where partial and progressive parathyroid lesions were present. MacCallum has made similar observations, the acute tetany giving place to a stuporous condition, which lasted several days before terminating in death. These observations have been confirmed by Thompson and Leighton, who, furthermore, have added that where the chronic symptoms trophic in nature arise, there is not uncommonly evidence of greatly diminished resistance to infection.

Anomalies of the Parathyroids

Variations in Position.—A considerable variation in the position, number and size of the parathyroids has been reported.

Variations in Man.—As normal for the human, we may take it that there are two pairs of these glandules, a set on each side, consisting of a superior and inferior body in close relation to the lobe of the thyroid. The superior parathyroid is most constant in its position, occupying a place along the posterolateral border of the thyroid, and a short distance below

the level of the pole. It is loosely connected with the thyroid capsule, and at times is found to lie outwardly displaced or in a downward direction, opposite the midportion of the lobe. Less commonly, the superior parathyroids are removed at some distance above the pole of the thyroid in the vicinity of the thyroid cartilage.

The inferior parathyroids are less fixed in their relation to the lobes of the thyroid. Usually found at the posterior and outer margins of the lobe and close to the tip, they are often displaced downwards, so as to lose contact with the thyroid and lie along the loose tissue near the carotid sheath (Schaper). Again, their position along the trachea may make it difficult to distinguish the glandules from lymph nodes, or scattered remains of thymus tissue. The close points of origin of the thymus and the inferior parathyroids, not uncommonly bring these structures into anomalous relation with each other. Thus, the inferior parathyroids, or accessory glandules to them, may be found within thymus tissue (Thompson, Verebely, Erdheim) and the reverse has also been observed in which the thymus tissue was found incorporated in the parathyroids.

Variations in Animals.—The parathyroids of lower animals are still less constant in their position than in man, this is particularly true of the inferior parathyroids, of the dog as well as the cat (Harvier and Morel), monkey (Vincent and Jolly) and rat (Erdheim). The dislocation of the lower parathyroids, or their accessory structures into the thymus is more often seen than in man, while the implantation of them into the structure of the thyroid is so frequent as to suggest for this a normal position. This intrathyroid glandule is identified with difficulty, and in the dog requires particular attention. In color and general appearance, the tissue may differ but little from that of the surrounding thyroid, while the demarcation of the two structures by the presence of a capsule may be all but wanting. MacCallum never found the human parathyroids imbedded in the thyroid gland as is not uncommonly seen in dogs. Thompson and Leighton observed a most irregular distribution of the parathyroids in dogs, scattered lobules of this tissue being found as far down as the bifurcation of the trachea. This is in agreement with our own experience. Gley also comments on the inconstancy of the position of the parathyroids, noting fourteen variations in the situation of the glandules in thirty-three dogs. Alquier found the parathyroids in their normal situation only nine times in fourteen dogs. Because of this great variation in position, it is evident that the greatest care must be exercised in drawing conclusions on experiments which have dealt with only the parathyroids in their normal position.

Variations in Number in Man.—The number of parathyroids also suffers variations to a considerable degree, and the symmetrical distribution is far from constant. One glandule may be present alone on one side with one, two or three irregularly arranged on the other. Accessory parathy-

roids are not as common in man as in lower animals. They are not uncommon in the rat (Erdheim), Togofuku having found in one instance as many as eleven. In man more than four glands are reported by Zuckerkandl, Chantemesse, Marie, Müller, Erdheim and others; more often a smaller number is reported. In a series of forty autopsies, in which a careful search for the parathyroids was made, Thompson found four glandules in thirty-three cases, three of which showed accessory parathyroids, three glands in four cases, two parathyroids in two cases, and an absence of parathyroids in one case. In none of the cases of this series were there any manifestations which could be attributed to the abnormal number of parathyroids. In one instance, MacCallum found five pairs of parathyroids in a case of gastric tetany. In a further series of sixty-four autopsies, he found four glands in thirty-six of these, three in ten, two in fifteen, and one in three. Petersen at times was able to find only one parathyroid, and in other cases two or three glandules, variously distributed at the poles of the thyroid. Erdheim in one instance found as many as eight. Rogers and Ferguson reported the complete absence of parathyroids in twelve cases out of fifty-four bodies examined. In the latter cases it is probable that these small structures were overlooked.

Variations in Number in Fetuses and Infants.—In case of the human fetus, or newborn infant, as in very young animals, it is difficult at times to differentiate the parathyroids because of the presence of small projections of thyroid tissue which not yet possessing a colloid secretion and a mature morphology may resemble very closely parathyroid tissue. Verebely found fewer than four parathyroids in six per cent of the cases studied (138). He never observed more than four. The usual size was 2 to 19 mm. long, 2 to 9 mm. broad and 1 to 4 mm. thick. Verebely states that small portions of the parathyroid may appear in the thyroid or thymus, and also that small islands of thymus tissue containing Hassall's corpuscles may be present in the normal parathyroids.

Variations in Number in Animals.—The inconstancy in number of parathyroids is still greater in lower animals than in man. Observations have been made with particular reference to the dog, in which it was not uncommon to find supernumerary structures. Gley and Leighton found as many as eight, while in one instance we isolated as many as twelve in an adult dog. The supernumerary parathyroids may be distributed about the thyroid lying externally to its capsule, and usually upon the posterior and lateral borders, but they may also appear buried in the substance of the thyroid or at times at some little distance from the lower pole. It is more common to find the accessory parathyroids towards and beyond the lower pole of the thyroid than at the upper poles or above this level. In the majority of instances it is necessary to confirm the macroscopic finding of the small glandule by microscopic study. Small islands of pinkish gray lymphatic tissue may be confused with true parathyroid tissue.

It is of interest that where the parathyroids are present in insufficient number those remaining show more or less compensatory hypertrophy. Such hypertrophy may simulate in one of these glands the so-called adenoma of parathyroid. This has also been observed in human cases following hemorrhage into one or more of the parathyroids, as well as in animals after partial parathyroidectomy (Alquier).

Inflammatory and Fibrotic Reactions in the Parathyroids

Acute Inflammations.—Acute inflammatory reaction within the parathyroids is very unusual, and very few observers have found sufficient evidence of this process to comment upon its occurrence and significance to these glandules. The tissues of the parathyroids do not appear to offer favorable conditions for bacterial localization, so that microörganisms, which are the main causative factor for exudative reactions elsewhere, do not find a satisfactory nidus in them. This does not exclude the possibility of the effect of bacterial toxins acting upon the parenchyma of the parathyroids, but such action does not induce true inflammation, but more commonly leads to degenerative changes with possible late alteration in the stroma. Guizzetti (*a*) claims to have observed a marked infiltration by mononuclear cells in two cases of tetanus. In two other cases he failed to find the reaction. Thompson studied five cases of the same disease, and was unable to determine any change. Garnier found normal parathyroids in a case of experimental tetanus.

Inflammation by Extension.—Occasionally, inflammatory reactions in neighboring tissues may involve one of the parathyroids. Under these conditions, clinical manifestations of altered function do not make their appearance, and the finding is accidental. The not uncommon lymphocytic infiltration of the thyroid occurring in its periphery, and involving the capsule, transgresses its boundaries and may extend to the border of the parathyroid. In consequence, the main change resulting in the parathyroid is a thickening of its capsule and stroma along with a slight lymphocytic infiltration. Similar inflammatory processes may advance upon one or more of the parathyroids from a cellulitis of the neighboring tissues of the neck.

Fibrosis in the Parathyroids.—Fibroses, to a greater or less extent, are found more commonly than can be accounted for as the outcome of acute or subacute parathyroiditis. In infants, the capsule and stroma of the parathyroids are very delicate, forming only a fine reticulum supporting the blood vessels and parenchymatous structures. With advancing age, there is a relative increase in the connective tissue stroma, as well as the adipose tissue which, however, does not normally proceed to a true fibrosis. In many adults, even in advanced age, the connective tissue structures

surrounding and permeating the gland remain quite delicate, save for the increase immediately about blood vessels, which appears to have a more direct relation to the circulatory apparatus than to the tissues of these glands. No significance is to be given to minor variations in the amount of stroma. It is only when the fine reticulum gives place to definite trabeculæ and bands that a state of fibrosis is accepted as pathological. With the increase in the connective tissue structures there is a distortion of the alveolar nests of epithelial cells, and a crowding of these elements into irregular chains and alveoli. Such increase of the connective tissue has been given the name of chronic parathyroiditis, or fibrosis of the parathyroid. Verebely has described two cases of this kind, and although the fibrosis was quite marked, there was no evidence that an inflammatory reaction had preceded it. Thompson followed the presence of progressive fibrosis in poorly nourished individuals, in association with chronic heart disease, cirrhosis of the liver and chronic tuberculosis. He points out, however, that many cases exhibiting these extraneous lesions show no evidence of fibrosis in the parathyroids. He lays more stress upon the presence of a concomitant connective tissue increase of the parathyroids, adrenals, thymus and thyroid, in cases of primary infantile atrophy. In this condition the parathyroids show change of a degenerative type which appears to precede the increase in the connective tissue stroma. He states that he does not wish "to imply that these glands are primarily at fault in infantile atrophy, but to emphasize the fact that failures of assimilation in this disease lead to wider changes than simple wasting of fat and muscle." It is of importance to note that where the parathyroids are slowly but progressively deranged with probable impairment of their function, tetany is not to be found, but that nutritional disturbances are more commonly seen. [It is of interest in this connection that attempts to produce experimental tetany by parathyroid extirpation not infrequently lead to similar results.—R. G. H.]

Obliteration of Parenchyma.—Where true fibrosis has made its appearance there is also more or less suppression of the glandular elements. Under these conditions, the close relation of the parathyroids to the capsule of the thyroid may lead to the development of intimate adhesions and partial obliteration of the parathyroid, so that the recognition of the involved glandule is obtained with difficulty. The fibrosis in the glandules may be quite unequal, marked lesions appearing in one, while the remaining glandules are quite free. With the evidence which is at hand, it would appear that the fibroid change is commonly not the outcome of a true inflammatory reaction, but the result of a hyperplasia of the connective tissue elements in consequence to antecedent alteration of the activity of the epithelial elements.

Parenchymatous Atrophy in the Parathyroids Following Thyroidectomy.—MacCallum observed that the removal of the thyroid of animals is

occasionally followed by an increase in the stroma, and a moderate atrophy of the parenchymatous cells of the parathyroids. In a case of epilepsy, Erdheim found some sclerosis of all of the parathyroids. However, in another instance, the glands were found to be normal, and he was unable to correlate the sclerosis with clinical manifestations. Forsyth (*a*) found marked sclerosis of the parathyroid in a case of myxedema with an atrophic thyroid. Others (Erdheim, Maresch, Peucker), studying cases of myxedema with congenital absence of the thyroids, found the parathyroids in their normal position and without specific lesions.

Parathyroid Involvement in Tuberculosis and Syphilis.—Occasionally the parathyroids may be the site of a tuberculous infection in association with a general miliary dissemination. Verebely, in a study of the lesions in 138 cases, found two involved in tuberculosis. Similar cases are also described by Benjamins, Eggers, Winternitz and others. Fibrosis, atrophy and hydropic degeneration of the parathyroids have been described by Haberfeld in two cases of congenital syphilis.

Degenerations in the Parathyroids

Intoxications.—Degenerations of organs are the outcome of the effect of chemical substances in solution, harmful to the tissue, or alterations induced by an inadequate nourishment. Both of these factors play a part in injuring the quality of the parathyroid structures. Acute and chronic intoxications, from local or disseminated infections, have their influence upon the parathyroids as they do upon the remaining ductless glands and other tissues. Occasionally, the intoxications associated with kidney retention in chronic nephritis, diabetes and cirrhosis of liver, give rise to parenchymatous degeneration of the parathyroids, which, although altering the morphological character and chemical constituents of their cells, rarely produce such advanced change as to interfere with function.

Circulatory Disturbances.—The anemias and leukemias are prone to cause chronic but progressive degenerations of the fatty type, with the deposition of extraneous pigments in the glandules. Progressive degenerations are also to be noted when spontaneous scleroses of vessels involve the circulations of the parathyroids (Fig. 1). It has been shown that when during the ablation of the thyroid the vessels of supply have been ligated, the parathyroids which remain behind suffer a process of atrophy until a compensatory circulation is reëstablished. Halsted claimed that the parathyroids are likely to be seriously encumbered by an inadequate circulation following surgical interference with the thyroid.

Acute Degenerations.—The recognition of acute degeneration of the parathyroid has been made in a limited number of instances. The small size of the gland does not permit of ready recognition with the naked eye

of such changes as cloudy swelling or parenchymatous degeneration. Occasionally, with the presence of acute infections and inflammatory reactions in the neck, the general edema which takes place in these tissues may also be found in the parathyroids. The glandules are slightly enlarged, rounder than normal and quite soft. They lose their yellowish appearance and assume a pinkish gray hue. Microscopically, edema may be demonstrated in a general loosening of the stroma, while the individual parenchymatous cells are enlarged, basophilic granules appear in the cytoplasm and the nucleus is more vesicular. Under these conditions, distortions of the architecture are easily exaggerated by post-mortem change. Plasma cells are found in the stroma in greater prominence and the alveoli show more than normal irregularity.

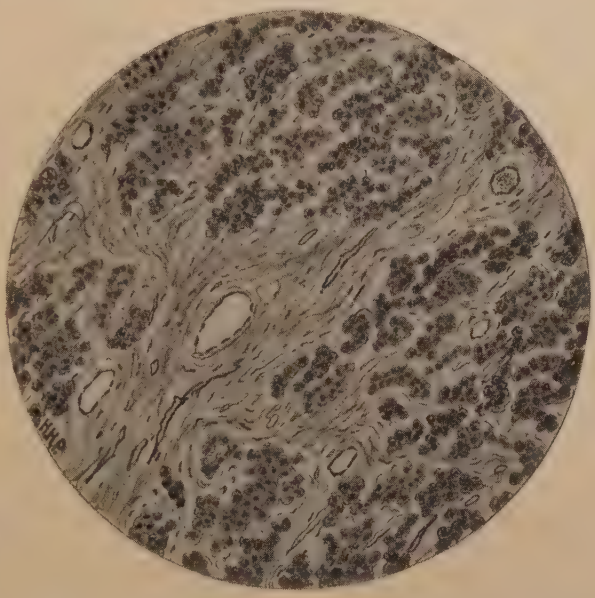


Fig. 1. Sclerosis of parathyroid, as occasionally met with in advanced age.

Fatty Degeneration.—It is recognized that the parathyroid glands contain a certain amount of demonstrable fat in their healthy condition. Early in life, however, little or no such fat may be found, and it would appear that with ascending age, accompanied by the usual diseases of advanced life, fatty change in the parenchymatous cells is not uncommonly seen. Although it would appear that fat tends to accumulate in larger quantities in the later years of life, the importance of its presence has not been determined. Occasionally, the parathyroids of the aged show less fatty materials than younger individuals. It is also found, that in cases in which the parenchymatous cells show fatty deposits, there is also a similar deposit in the stroma. Under these conditions the stroma is relatively increased in amount, and has assumed a hyaline appearance of its collagen fibers. These variable deposits of fat in the parenchymatous cells bear no definite relation to the appearance of manifestations of altered function. Hence the mere presence of fat in the parathyroid is, in itself, not indicative of an incompetent gland. Müller drew particular attention to the occurrence of fatty change of the parenchymatous cells.

As is so often observed in other tissues and organs, the parathyroids may show evidence of nutritional disturbances when serious lesions involve other structures. Fatty degeneration may involve the parathyroids without destroying their secretory ability in cirrhosis of the liver, chronic nephritis, chronic tuberculosis, diabetes and pyelonephrosis (Thompson and Harris). These authors have found that the parathyroids are apt to show fatty change when an acute infection is superimposed upon a chronic one. This was particularly marked in five cases of ascending infection of the genito-urinary tract. They have also observed the presence of marked fatty change in four cases of infection of the gall bladder and ducts associated with extreme jaundice. In malignant disease and in syphilis of long standing, fatty change of the parathyroids is encountered in variable quantity. The same is also true in pernicious anemia and the chronic blood diseases. There is no evidence that the parathyroids primarily suffer serious degeneration of the fatty type. The condition appears to arise as a process secondary to systemic derangements. Bauer claims to have noted a diminished fat content of the parathyroid tissue in cases of adenoma of the parathyroid with osteomalacia.

Colloid Degeneration.—Comment has been repeatedly made on the occurrence of colloid degeneration of the parathyroid. In some instances, the authors have referred to the presence of small masses of colloid material lying within the glandular portion, while others have referred to a disturbance of the alveolar arrangement by the presence of small quantities of homogeneous material, and an alteration of the stroma to assume a hyaline appearance. The presence of colloid within the alveoli is not uncommon in individuals above twenty years of age. In the young, as well as in a certain number of individuals in middle life, the complete absence of any colloid is normal. At times the gland tissue shows large numbers of the alveoli with sufficient colloid in their centers to give them the appearance of small acini, with the epithelial cells crowded along the periphery as is seen in thyroid tissue. The presence of this colloid storage has led some to assume that the parathyroid was adopting the qualities of thyroid tissue, and that its change was the result of an unusual demand following functional disturbance of the thyroid. Where extirpation of the thyroid has been undertaken, and the parathyroids have shown the presence of colloid within their acini, it has been interpreted as indicating a compensatory function. But evidence is still lacking that a parathyroid can participate in the activities of the thyroid. The presence of colloid within the alveoli need not be viewed as a process of degeneration, but one within the normal character of these glands. When, however, the accumulation is of undue quantity, and leads to cystic dilatation of the acini, as well as the merging of several neighboring structures with each other, and at times accompanied by hemorrhage, we are then dealing with a pathological process. The colloid that makes its appearance under these condi-

tions appears to be normal in its character, and it has not been possible to differentiate the quality of the secretion from that found in the glands with normal secretion. It is not necessary to assume, as have Forsyth, Vincent and Jolly, that because the parathyroid, with its colloid deposits, simulates in appearance the thyroid tissue, a true metamorphosis of function to that of the thyroid has occurred.* Thompson and Harris observed a case in which the similarity between the small parathyroid acini with those of the neighboring thyroid was so great that it was impossible to determine the line of demarcation. The capsule separating the two tissues was merged with the stroma of each, and could not be clearly differentiated from the scattered trabeculæ. Occasionally, the accumulation of considerable quantities of colloid material within the epithelial structures is accompanied by a degeneration of the stroma of hyaline or colloid type. Where the cells bounding the acini have degenerated and are found lying scattered amidst the colloid material, it would appear as if the colloid content of the alveoli had a relation to the degenerative changes taking place in the stroma. In this again, the process within the parathyroids resembles that seen in the thyroid. Where marked colloid degeneration has taken place, the epithelial cells are also found to contain small globules of colloid material in their cytoplasm. These degenerations are found in cases both with and without manifestations of parathyroid deficiency.

Other Degenerative Findings in the Parathyroids.—Thompson (*b*) studied the parathyroids in twelve cases of marasmus, in infants under one year of age. He found that the parathyroids were quite uniformly diminished in size, and showed a condition of degeneration of the essential cells of the glandules. Concurrently with the atrophy and degeneration, there was a relative and actual increase in the connective tissues, so that a moderate fibrosis was readily demonstrated. He believed that these changes within the parathyroids were the result of the marantic condition, rather than its cause. It was observed that the changes within the parathyroids were comparable to changes observed in the other endocrin glands.

Petersen states that degenerative changes are not uncommon in the parathyroids, particularly in individuals of over twenty years. The character of the degeneration was not constant, but included cloudy swelling, atrophy with fatty change and a condition of cystic degeneration in a fair number of instances. These degenerations make their appearance independent of clinical manifestations with which they may be associated. It would appear that various responses occur within the parathyroid which do not incapacitate the glandules to a degree to give rise to a constitutional reaction. There appears to be a considerable reserve of function, which is only overstepped when the tissues suffer sudden derangement or when the progressive lesion oversteps the bounds of systemic demands.

* Vincent has recently expressed doubt as to the validity of his former position. R. G. H.

A variety of degenerations was observed by Benjamins. These included atrophy with pigmentation, replacement fibrosis, colloid degeneration of stroma and hydropic degenerations, which in his cases were at times associated with the presence of goiter. Erdheim frequently noted the presence of glycogen and colloid. He also found small cysts present in the glandules, the parenchymatous cells of which showed degenerative changes. Verebely, on the other hand, observed the presence of fat, glycogen, hyalin and pigment in the normal parathyroids. He also observed that small cystic dilatations of the acini, with or without colloid content, may be present in the normal glands. He found, too, that the cysts vary considerably in size, and commonly contain a mass of colloid material not unlike that observed in the thyroid. These cysts are usually surrounded by oxyphil cells. Only occasionally did he observe, and this particularly in small children, small quantities of blood within these cysts.

Hemorrhage into the Parathyroids

On Clinical Tetany.—Of late years, the study of infantile tetany has given considerable prominence to the occurrence of hemorrhage into the parathyroid glandules. The possible relation between the parathyroids and tetany in adults was first suggested by Jeandelize, and later this was emphasized by Pineles and Chvostek for various types of tetany and tetanoid conditions. Erdheim was the first to demonstrate a lesion in the parathyroids of infants which was sufficiently severe and constant to merit attention. In two children, with marked tetany, he found extensive hemorrhage into the glands, and shortly following this, his colleague, Yanase, made similar observations on two further cases. Subsequently, Haberfelt, working in the same clinic, carefully analyzed seven fatal cases of tetany and was able to demonstrate recent hemorrhage, blood cysts and blood pigment in six of them. In one case there was complete absence of either recent or old hemorrhage.

Hemorrhage Not Associated with Tetany.—Other observers have likewise found hemorrhages into the parathyroids, but have not always been able to correlate their presence with tetany or tetanoid manifestations (Verebely, Koenigstein, Thompson, Petersen and Thiemich (*c*)). The majority of cases of tetany occur during the first year of life, and it is at this time when hemorrhage into the parathyroids is to be found. These hemorrhages are of all gradations, from slight local leakage of the vascular sinuses to the extensive infiltration of the gland and an obliteration of the functional tissue. It is not clear as to the manner in which the hemorrhages are brought about, and it would appear that they are prone to take place at the time of birth, or a short time preceding it. All four glandules may be attacked simultaneously, but in other instances only

one or more are involved. When the hemorrhages are slight, absorption of the extravasated blood takes place, leaving behind little or no evidence of its occurrence, or again, the removal of the blood may be accompanied by deposition of the pigments which will remain for considerable periods of time.

Erdheim and his school claim that the hemorrhage leads to such distortion of the parathyroids and their function that a state of hypoparathyroidism is induced. The deficient parathyroid activity has as a sequel, disturbed calcium metabolism with increased calcium excretion, as demonstrated by MacCallum and Voegtlin.

Hemorrhage Secondary to Degenerative Processes.—In not a few cases of hemorrhage, secondary processes of degeneration—fatty, colloid and hydropic—take place, and, furthermore, fibroses and atrophy of the glandules are later to be observed. The manifestations of tetany may occur during any of these periods, at a time when hypofunction of a sufficient grade has occurred. It is evident, of course, that hemorrhage into the parathyroids is to be encountered in greater frequency in infants of tender age than are instances of tetany. There is, however, no adequate explanation for the occurrence of hemorrhage. It would seem that the parathyroids of the fetus late in pregnancy, as well as of the newborn child, are susceptible to some mechanical or circulatory factor making hemorrhage into them easily induced. Later in life this is but rarely seen. A single case is reported by Diller wherein, following a severe accident, tetany developed one week later. At autopsy all of the glandules showed extensive hemorrhage. In the remaining number of the rather infrequent cases of adult tetany, hemorrhages have not been observed, but various authors have commented upon a state of atrophy, fibrosis or degeneration as the cause of an assumed deficient function of the parathyroids. It is suggested that these late cases of tetany have their inception in hemorrhage at an early period of life, and that the incompetency of the parathyroids makes its appearance only when the progressive degeneration has destroyed a considerable bulk of the glandules.

Our present knowledge of infantile tetany requires the addition of further study, to explain the vagaries which appear in the lesions of the parathyroids. We are still at a loss to explain the occurrence of the hemorrhages, and it would appear as if a further secondary factor were necessary to bring about a state of tetany, even when hemorrhage and other lesions occupy these glands. In a certain number of instances, the hemorrhage appears to be a late event in the disease, occurring in conjunction with petechial hemorrhages of other tissues. Parathyroid hemorrhages also occur incidental to acute and chronic nephritis, acute bacterial intoxications, syphilis and severe blood diseases.

Tumors of the Parathyroid

Primary Neoplasms.—True tumors of the parathyroid are indeed rare, and very few reports of them are found in the literature. The majority of the cases which have been reported have been described as adenomata, while malignant types of tumors have been observed by only a few men. There is still discussion concerning the nature of many of these benign adenomata, inasmuch as some claim that the tissue mass represents a process of hyperplasia, rather than a true neoplasm. These benign tumors usually consist of small nodules from two to four centimeters in diameter, which occupy a part or whole of the involved glandule (Fig. 2). It is possible that, as in the thyroid, these small tumor masses would be found with greater frequency if systematic examination of the structures were undertaken at every autopsy. It is unusual to have a search made for the parathyroids at autopsy, unless some clinical manifestations, or an interest in a specific problem, urges the pathologist to spend sufficient time to uncover them, and to make proper microscopical observations. It is only when the parathyroid has attained, through tumor, a sufficient size to give rise to a projecting mass at the borders of the thyroid that adequate attention is given.

Fig. 2. Adenoma of parathyroid, comparable to a diffuse hyperplasia.

Since the parathyroids normally lie, not only along the posterior border and towards each pole of the lobes of the thyroid, but also they may be buried to a greater or less depth amidst the tissues of the thyroid, it is possible that aberrant change and tumor formation may readily occur and go unrecognized. Under the conditions of hyperplasia and benign tumor formation, the parathyroid glandules assume a variety of characters sometimes quite different from that of the normal tissue, and although not resembling the normal thyroid tissue, may be confused with

the many changes which the thyroid adopts in its protean morphology. The extrathyroid tumors of the parathyroid origin can be recognized with greater certainty than those which occur in the thyroid tissues, and it is the former group upon which most tress must be laid. The clear differentiation between adenomatous hyperplasia and true neoplastic adenoma presents much greater difficulty. In this we have a problem somewhat similar to that observed in the pituitary, where all gradations between a general overgrowth of the glandular elements in a process of hyperplasia, and a circumscribed nodule receiving the name of adenoma, occur. When such masses become of considerable size, they cause secondary distortions within the gland and its surroundings. A line of demarcation between such hyperplasia and true adenoma can hardly be made. This is also true for the parathyroids, although in these glandules circumscribed areas of adenomata are at times found separated from a small portion of remaining normal parathyroid tissue.

The following tumorous masses, as outlined below, have been described as of parathyroid origin.

Observer	Date	Sex	Age	Characteristics	Remarks
De Santi	1900	M	58	Hemorrhagic; intrathyroid.	Parathyroideal in appearance.
Benjamins	1902	M	57	Extrathyroid; nonmassive.	Pressure symptoms.
Erdheim	1903	M	18	Small adenomal type.	
Hulst	1904	F	Old	Small circumscribed intrathyroid.	Parathyroideal in appearance.
MacCallum	1905	M	26	Circumscribed.	Similar to a parathyroideal adenoma.
Weichselbaum	1906	F	Old	Adenoma left parathyroid.	
Verebely	1907	F	42	Diffuse adenoma.	Associated with osteomalacia.
Thompson and Harris	1908	F	33	Large intrathyroid.	
DaCosta	1909	F	32	Large parathyroid adenoma.	
Erdheim	1911	F	45	Adenoma of parathyroid.	
Thompson	1911	F	32	Cancer of parathyroid.	Secondary-breast.
Mollineus	1913	F	38	Adenoma.	Associated with osteomalacia.
Mollineus	1913	F	59	Adenoma.	Associated with osteomalacia.
Harbitz	1915	F	75	Multiple adenoma.	Associated with paralysis agitans.

In 1906 Askanazy (*b*) reported an adenoma of the parathyroid as did Verbitz. The case of Verbitz presented the characteristics of diffused adenomata. A year later, in 1907, Langhans (*b*) reported nine cases, five of which were previously described by Kocher as parastruma. There are some of these cases which cannot, however, be accepted unreservedly as

parathyroid tumors. In 1919 Ewing reported a case without any details. Other tumors have been described by de Paoli, Pepere (*a*), Claude and Schmiergeld, Makai, Walther, and Bernard Alamartine.

As is evident from these reported cases, it is not clear that all of them represent masses arising in parathyroids, nor that those which have occurred within the glandules are to be considered in terms of neoplasm as we find it elsewhere. The frequency with which all of the parathyroids are involved in enlargement, suggests that a functional demand has led to the compensatory hyperplasia. In not a few cases, such hyperplasia, or even true tumor, shows an alteration in its internal structure with increase of stroma, the development of hyaline bands about the vessels, and the presence of colloid within the acini, making them resemble quite closely nodules of thyroid origin. Depending upon the extent of these microscopic alterations, we find increasing difficulty in establishing satisfactory differentiation, particularly when the aberrant nodule lies within, or is closely attached to the thyroid. The tumor described by Benjamins and some of those of Langhans and Kocher are given as examples of malignant parathyroid tumors.

Fig. 3. Cysts of parathyroid.

Cysts.—Cysts of the parathyroids are not uncommon, and at times are of such size as to lead to an enlargement of the gland to make it resemble tumor. The tissue surrounding the cyst may be compressed and have evidence of an increase in the stroma. Inflammation is usually wanting and seems to bear no relation to their occurrence. All gradations of cystic change are to be found and a study of the parathyroids of individuals from the age of twenty reveals the fact that these lesions are of very common occurrence. Many of them are of microscopic size, and illustrate small acini with well developed lumina containing colloid (Fig. 3). One or more of these may enlarge, to crowd out the neighboring parenchyma and fuse with contiguous cavities. Some authors speak of this as a type of cystic degeneration, and emphasize the presence of fatty change and

hyaline degeneration of the stroma in support of this. In similar cases, the arterial walls show bandlike hyaline structures or deposits which have been referred to in the literature as amyloid. It is unusual to obtain chemical reactions for amyloid. Cysts which have developed from the colloid containing acini may continue to enlarge and subsequently contain a thin serous fluid. These are subject to hemorrhage as are those of the thyroid. The epithelial cells, responding in hyperplasia or tumor formation, as well as those lining the cysts, are the basophilic, normally forming the chief elements of the glandules. These cells may be arranged in nests, rows and columns, or they may appear in aggregations in which many of the centrally lying cells do not appear to rest directly upon the stroma. Vacuolation and hydropic degeneration of the parenchymatous cells is not uncommon. Less commonly, cysts may take origin from lymphatics, remnants of congenital parabranchial tubules and implantation masses of thyroid or thymus.

Metastatic Tumors.—The metastasis of secondary malignant tumor into the parathyroid glands is still less frequent than the development of primary tumors. Only a few cases have been recorded. The first of these was by Koenigstein, who reported a metastatic adenocarcinoma which involved a considerable region of the neck, including all four parathyroids. Three of these glandules were so disturbed that nothing remained of their normal structure. Koenigstein remarks upon this extensive infiltration and the absence of any manifestations of tetany. Pepere (*a*) observed the infiltration into the parathyroid tissues of a malignant growth arising in the thyroid. In a second case, the same author reports upon the occurrence of metastases from a cancer of the breast. Thompson (*c*) also reports two cases, the first occurring in a woman of thirty-two, who died of extensive carcinomatosis following cancer of the breast; in this instance all four parathyroids were occupied by metastatic growths. The second case was a male aged sixty-seven, who died of mediastinal lymphosarcoma, in whom three of the four parathyroids were occupied by secondary tumors. The author also noted the absence of any signs of tetany in both of these cases. These findings, he states, bear out the experimental work in which it has been shown that the parathyroids may be gradually destroyed without symptoms of tetany.

The Parathyroids and Bone.—*Relation to Calcium Metabolism of Bones and Teeth.*—A considerable relationship has been suggested between the functional activity of the parathyroid and the quantitative distribution of calcium salts in the body. It has further been observed by Kassowitz that tetany in children is not uncommonly associated with rickets, in which improper metabolism of calcium salts may otherwise be demonstrated. Erdheim observed that the extirpation of the parathyroids of rats leads to the development of imperfect teeth (incisors), poor in calcium. In later experiments, it was still further shown that

the dentine developing subsequent to the extirpation of the parathyroids showed little or no calcification. This was found true not only for the teeth, but also for bony structures. Fractures of bone occurring subsequent to the removal of the parathyroids failed to heal by osseous union and showed a lack of calcification. Under these conditions, where the animal survived a considerable period of time, the bony structures lost some of their calcium salts, becoming more elastic and resembling bones observed in osteomalacia. Bauer associates the presence of osteomalacia in a human case with the presence of an adenoma of the parathyroid. Fleischmann compares the results obtained in the experimental animals with the somewhat similar changes observed in rickets. In the human cases there is not only a deficiency in the bone production and the process of calcification, but a similar lack of calcium precipitation is found in the teeth. Escherich suggested functional deficiency of the parathyroids and congenital parathyroid hypoplasia as factors related to the occurrence of rickets. This relation was assumed but not demonstrated, the assumption being based on the frequent coincidence of tetany during the progressive stages of rickets. The suggestion found some support in the evidence of calcium deficiency in the dentine of the molar teeth in experimental animals in which the parathyroids had been removed (Erdheim, Fleischmann). A study of four cases of rickets, by Schmorl, showed no lesions in parathyroids.

In 1906, Askanazy reported upon a case of osteitis deformans without osteoid tissue, in which the left lobe of the thyroid was involved in a tumor resembling a new growth arising from the parathyroid. Osteomalacia was not present. Subsequently, Schmorl examined four cases of osteomalacia, and in only one of them found an adenomatous hyperplasia in the parathyroids. In the other three these glandules appeared normal. Strada observed a hyperplasia and enlargement of the parathyroid in a case of osteomalacia, which was thoroughly studied. It is interesting that in this group of cases, the hyperplasia of the thyroid was associated with altered calcium metabolism leading to defective bony development.

The Parathyroids and Paralysis Agitans.—In 1885, Horsley observed that when the thyroid was completely removed, a remarkable train of symptoms, beginning as slight fibrillation of the muscles of the hands and feet and progressing to a constant tremor, made their appearance. These tremors persisted until shortly before death. Horsley believed that these observations were of importance, as tending to explain the causation of the constant tremor seen in paralysis agitans. At the time of Horsley's work the existence of the parathyroids as functional entities was not recognized, and it is probable that the thyroidectomy reported included the removal of the parathyroids. Similar observations made by Langhans, and, subsequently, Berkeley and Lundborg brought forward the

theory of the development of paralysis agitans through insufficiency of parathyroid function.

Thompson (*a*) studied the parathyroids in nine cases of paralysis agitans. The parathyroids, from three to five in number, were found in all cases. He was unable to determine any particular lesion in these cases which would differentiate the conditions found in the parathyroids from those observed in cases not suffering from paralysis agitans. The glandules were slightly smaller than usual and there was some increase in the stroma of the glands. As this condition is commonly met with in elderly individuals, no significance can be attached to the finding of early fibrosis, slight atrophy and fatty change. In fact, microscopical study of the glandules in Thompson's cases showed no variation from what might be expected in normal individuals of this age. Similar negative findings in three cases were reported by Erdheim. Harbitz reported a case of paralysis agitans possessing symmetrical tumors of the parathyroid which, clinically, caused no local disturbance. He does not believe that it had an etiological relation to the disease.

Clinical Syndromes Due to Disorders of the Parathyroid Glands . . . . . *Lewellys F. Barker*

Introduction—Historical Notes—Symptomatology—Tonic Contractions of Muscles—Increased Mechanical Excitability of Motor Nerves—Increased Electrical Excitability of Motor Nerves—Increased Excitability of Peripheral Sensory Nerves—Increased Excitability of Nerves of Special Sense—Autonomic Disturbances—Psychoses—Tetany and Epilepsy—Tetany and Myotonia—Reflexes—Sensory Tetany—Skin—Muscles, Bones and Joints—Endocrin Glands—Metabolism—Etiology and Pathogenesis with Comments upon Its Different Forms—Idiopathic—In Diseases of the Digestive Tract—In Association with Infectious Diseases—In Association with Intoxications—In Association with Menstruation, Pregnancy and Lactation—After Operations for Goiter—Tetany in Children—Experimental Production in Human Beings—Unitary Conception of Tetany—Poisonous Substances in Tetany—Site and Mode of Action of the Tetany Poison—Pathological Anatomy and Histology—Course and Termination Prognosis—Prognosis in Childhood—After Strumectomy—In Idiopathic Tetany and in Infections and Intoxications—In Tetany Associated with Gastro-intestinal Diseases—In Maternity Tetany—General Diagnosis—Differential Diagnosis—From Other Conditions in Which Hyperkinetic Phenomena Resembling Those of Tetany May Occur—From Other Conditions That May Simulate the Motor Paresis Seen in Tetany—From Conditions with Sensory Phenomena Resembling Those of Tetany—Prevention—Treatment—Organotherapy—Pharmacotherapy—Hydrotherapy and Thermotherapy—Electrotherapy—Mechanotherapy—Climatotherapy—Occupational Therapy—Serotherapy—Dietotherapy and Other Measures—Surgical Therapy Other than Organ Transplantation—Parathyropathies Other than the Hypoparathyroidism of Tetany—Osteopathies and Neuropathies of Postulated Parathyropathic Origin—Hyperplasia of Parathyroid Glands in Chronic Renal Disease.

CLINICAL SYNDROMES DUE TO DISORDERS OF THE PARATHYROID GLANDS

LEWELLYS F. BARKER

BALTIMORE

(a) Tetany

I. Introduction

Tetany is a clinical syndrome characterized by a *peculiar hyperexcitability of the nervous system* (*motor, sensory and autonomic*), and, in manifest cases, also, by spontaneous *attacks of peculiar tonic spasms,* involving certain groups of muscles, or even the whole body musculature.

The syndrome can be easily and surely recognized, in all cases, by demonstrating the existence of its most constant and characteristic mark, namely increased response to galvanization of the motor nerves (*Erb's phenomenon*).

Clews to the existence of the syndrome include also certain responses of the motor nerves to mechanical stimulation. Thus, pressure on the nerves in the bicipital sulcus gives rise to a peculiar "obstetrical" attitude of the hand and forearm (*Trousseau's phenomenon*); tapping the facial nerve causes contractions of the muscles on the corresponding side of the face (*Chvostek's phenomenon*); stretching the nerve trunks of the extremities causes peculiar localized contractions of the muscles of these extremities (*arm and leg phenomena* described by Ferenczi, Pool, Schlesinger and others).

In the severer cases, tetany manifests itself by spontaneous *attacks of intermittent tonic contractions* of certain groups of muscles. These spontaneous tonic spasms are often painful, and tend to be limited to groups of muscles innervated by certain nerves (brachial; lumbosacral), so that in the patients' extremities, *definite attitudes* (obstetrical hand; extension of knee with extreme supination of the foot; carpopedal spasm) are assumed during the attacks. Though usually bilateral and symmetrical, the tonic spasms may affect one half of the body only (*hemitetany*). Cramps may occur also in the laryngeal muscles (laryngospasm), in the face and jaw muscles (facial spasm; trismus), occasionally in the tongue,

in the muscles of the neck and trunk, in the eye muscles, in the diaphragm and, rarely, in the autonomically innervated smooth muscle of the viscera (bronchi, heart, digestive apparatus, urogenital apparatus). These attacks of tonic spasm are not, as a rule, accompanied by loss of consciousness. Their duration is variable; they may last from a few seconds or a minute to a few hours or even a few days.

The *hyperexcitability of the sensory nerves* is manifested by: (1) pains in the muscles during the spasms, (2) paresthesias, especially in the distal parts of the extremities, and (3) increased response to electrical and mechanical stimuli applied to the sensory nerves (Hoffmann's phenomenon).

Flaccid or spastic *paresis* of the lower extremities may follow the tetanic seizures or may appear as equivalents of them. *Disturbed mental states* and *epilepsy* are sometimes associated with tetany.

When the attacks of tetany occur spontaneously, the tetany is said to be *manifest;* otherwise it is said to be *latent.*

Tetany may occur in *epidemic* form. It is *endemic* in certain places (notably in Vienna and in Heidelberg). *Sporadic* cases of tetany may occur anywhere.

The syndrome of tetany may be *acute* or *chronic.* In chronic tetany, vasomotor phenomena, secretory phenomena, and trophic changes are common. Among these may be mentioned dermatographism, hyperidrosis, polyuria, intermittent swelling of the joints, local edemas of the hands and feet, loss of the hair and of the nails, defects in the enamel of the teeth, and early cataract in the eyes.

Tetany may occur at any *age.* Thus it affects both adults (*tetania adultorum*) and children, either sucklings (*tetania infantum*) or older children (*tetania puerorum*).

The syndrome is very common in children that have rickets, and in these children laryngospasm is one of the commonest symptoms. The identity of tetany and the spasmophile diathesis of children is maintained by many pediatrists.

In adults, *several "forms" of tetany* have been described according to the several different conditions with which it may be associated. Thus, tetany may accompany certain diseases of the digestive apparatus (*tetania gastrica, tetania colonica*); or it may occur in combination with the processes of maternity, either during pregnancy or during the lactating period (*tetania gravidarum, tetania lactantium*); or it may develop in the course of certain *infections or intoxications;* or it may appear after operation for goiter (*tetania strumipriva*). Sometimes it develops in persons otherwise apparently healthy (*tetania idiopathica, epidemic-endemic tetany, tetany of workmen*).

Tetany occurs in *both sexes,* though certain forms of tetany occur predominantly in males, other forms predominantly in females.

Tetany is especially common at certain *seasons* of the year, especially in the late winter and early spring. Thus, in places in which the disease is endemic, it often becomes epidemic during the so-called "tetany months" (March and April).

The occurrence of the syndrome of tetany appears, in many cases at least, to stand in a definite *relation to abolition of, or to insufficiency of, the functions of the parathyroid glands.* Thus, it has been shown that, if the parathyroid glands be removed in animals, the operation is followed by the development of a severe, indeed a fatal, form of tetany (*tetania parathyropriva*). It has been demonstrated also that the tetany that follows strumectomy in human beings is due to removal of, or injury to, the parathyroid glands; in other words, tetania strumipriva is a tetania parathyropriva. And it is now believed by many, though by no means by all students of the subject, that the syndrome of tetany in all its forms, and whether occurring in children or in adults, is always due to loss of function, or at least to diminution of function, of the parathyroid glands. Though this unitary conception of the pathogenesis of tetany is probably true for several forms, it must be admitted that the definite proof of it has not yet been brought for certain of the forms of tetany.

Why the nervous system should become more excitable when the parathyroid function is deficient is not yet known, though it has been thought probable that, during hypoparathyroidism, some chemical substance (*hypothetical tetany toxin*) that is poisonous to the nervous system develops, or is permitted to accumulate, or remains unneutralized, in the body, and that the tetany syndrome is due to intoxication by this substance.

Interesting studies of *intermediary and end metabolism,* in patients suffering from tetany and in animals in which tetany has been produced experimentally, are now being prosecuted in the hope that further clews to the etiology and pathogenesis of the disorder may be discovered. The demonstrations of the occurrence in tetany (1) of disturbances of the acid-base equilibrium (acidosis; alkalosis), (2) of deficiency of sedative ions (calcium and magnesium) and of excess of irritating ions (potassium and sodium) in the tissues, and (3) of the excretion of guanidin and guanidin derivatives in the urine, are all interesting in this connection, as are (4) certain experiments bearing upon the ferments produced by the parathyroid glands, (5) those dealing with the relations of thymus function to parathyroid function, (6) those revealing that tetany can be produced by forced respiration, and (7) those concerned with the influence of diet, of occupation and of environment, upon the occurrence of tetany.

The *treatment* of tetany is as yet unsatisfactory. With our newer knowledge, however, much can be done to prevent the occurrence of tetany, and researches by both medical and surgical methods, actively carried on, have resulted in the discovery of several helpful therapeutic measures.

Changes of diet, of occupation, and of surroundings, the control of intoxications and of infections, the administration of calcium salts, the exhibition of parathyroid substance and of parathyroid nucleoprotein, and the transplantation of parathyroid glands are the means of cure and of amelioration thus far devised that have proved most serviceable.

II. Historical Notes on Tetany

To understand the present status of any subject in clinical medicine, an acquaintance with at least the broad general outlines of the historical development of that subject would seem to be necessary. I shall, therefore, endeavor to explain, as briefly as is compatible with some degree of order and perspicuity, the way in which our present knowledge of tetany has gradually evolved.

If we leave out of account certain vague references in the writings of the ancients to muscle spasms that may have been tetany, we must admit that British observers were the first to recognize the syndrome of manifest tetany. It was on children rather than on adults that these first definite observations of the occurrence of the tonic spasms of tetany were made. Clarke, in his "Commentaries on Some of the Most Important Diseases of Children" (1815), discussed spasm of the glottis and called attention to the rigidity of the extremities that complicates this affection. It is especially interesting that, in this first report of spasms now recognizable as having been due to the tetany of childhood, one of the most characteristic features of infantile tetany, namely laryngospasm, was described. In the year following Clarke's publication, Kellie, of Leeds, contributed a paper to the *Edinburgh Medical and Surgical Journal* entitled, "Note upon the Swelling of the Back of the Hand and of the Foot and upon a Spasmodic Affection of the Thumbs and Toes which Frequently Accompanies It," in which he described what we now know must have been tetany. In his paper, Kellie also makes reference to spasm of the glottis as a part of the syndrome.

The medical writers of Continental Europe remained for a long time unacquainted with these early British observations. Thus, German authors have usually given the credit for the first recognition of the syndrome now known as tetany to Steinheim, a general practitioner in Altona, who, in 1830, described the condition as a "rare form of acute articular rheumatism." French authors, on the other hand, have attributed the first observation of tetany to Dance, who, in 1831, described the condition as "intermittent tetanus." But one Frenchman, B. Oddo, of Marseilles, who in 1896 wrote a careful review of the history of tetany, recognized the priority of the British observers and gave Clarke and Kellie the credit for its discovery.

* 1855. page 406

Though France no longer claims priority for the earliest observations of tetany, still she has the right to emphasize the great importance of the contributions of French medical men in the form of accurate clinical descriptions of the disease in several of its forms. Dance's paper dealt with tetany in the adult, not with tetany in the child, and, in the year following Dance's publication, Tonnelle described tetany in children, in a paper entitled "Upon a New Convulsive Affection of Infants." This writer described the contractures in the extremities of children and spoke of the affection as being relatively benign. He believed that the nervous excitability of childhood strongly predisposes to this syndrome, and he laid stress, also, upon disorders of the digestive apparatus as a cause. The value of tepid baths in the treatment of tetany, too, was emphasized by Tonnelle; indeed, his paper as a whole must be regarded as a valuable early contribution to the literature of infantile tetany.

During the succeeding fifty years, a number of papers were written by French authors upon tetany. These papers contributed to the terminology as well as to the clinical features of the disease. Tetany was described at this period under the term "essential contractures." The present name, "tetany," we owe to Corvisart, who wrote a thesis on the subject in 1852. Those interested in the history of tetany should read the report of a discussion of the disease, in which several eminent clinicians participated, at a meeting of the *Societé médicale des hôpitaux,* held in Paris in 1875. During this discussion the speakers established the relations of some cases of tetany to infections like typhoid and dysentery, and of others to digestive disturbances. The occasional epidemic character of the affection was also made clear, for several epidemics were definitely referred to. But above all, it is interesting that Trousseau took part in this discussion. After stating his ideas of the rheumatic nature of the affection and of its relation to lactation—he called the syndrome "nurses' contracture"—he also reminded his hearers of his own really great contribution to the subject, of the sign that still bears his name, namely the contractures in the hand and forearm that can be elicited, in latent tetany, by applying a ligature to the arm above the elbow. These terminological and clinical descriptive advances made by French physicians were of fundamental importance in the development of our knowledge of this strange malady.

From the middle of the nineteenth century on, clinicians in Germany and in Austria made noteworthy contributions to our knowledge of tetany. Especially between 1870 and 1890 were observations of great importance recorded. Thus, in 1871 and 1872, Kussmaul (*a*)(*b*) first called attention to the peculiar convulsive states that sometimes accompany dilatation of the stomach; his observations on gastric tetany were followed by confirmatory reports from other physicians. In 1874, Erb, of Heidelberg, made his careful study of the electrical hyperexcitability of the motor nerves, a

phenomenon now generally recognized to be the most constant of all the signs of tetany. In 1878, Chvostek, senior, of Vienna, described the mechanical hyperexcitability of the motor nerves in tetany, giving the "facial phenomenon," especially, a permanent place in the semeiology of the affection. It was somewhat later, in 1888, that Hoffmann (*a*) described the increased response also of the sensory nerves to electrical and mechanical stimuli. Thus, all four of the well known signs of latent tetany —Trousseau's phenomenon, Erb's phenomenon, Chvostek's phenomenon, and Hoffmann's phenomenon—were described in the four decades preceding the year 1890.

About 1880 tetany began to be very prevalent in Vienna and it is not surprising, therefore, that during the last two decades of the nineteenth century many important contributions to our knowledge of the subject were made by Viennese physicians. Perhaps the most important of these, aside from the excellent clinical descriptions of Chvostek and of von Frankl-Hochwart, was the observation by Weiss (*a*) in Billroth's clinic of the occasional appearance of tetany in patients after operations for the removal of goiter. Though Weiss was wrong in his idea that the tetany after strumectomy is due to injury to the sympathetic nerves at the operation, his observations upon the occurrence of 'tetania strumipriva' were the starting point of a whole series of important clinical and experimental investigations upon the relations of tetany to the thyroid gland and to the structures in its neighborhood.

It is an interesting coincidence that during the same year, 1880, in which Weiss's publication appeared, a Swedish observer, Sandström, described the existence in human beings and in certain mammals of certain structures that he described as "hempseed-sized glands near the thyroid gland." No one had a glimpse of the idea at this time, however, of the importance that this temporarily unnoticed discovery of Sandström's was, later on, to have for the pathogenesis of tetany. For at least ten years after Sandström's discovery, tetany and these 'parathyroid glands' were studied entirely independently of one another and without the slightest guess that they were in any way related to one another.

In 1890, an experimental physiological research that marks an epoch in the history of our subject emanated from France. Gley (*a*) of Paris, in that year, called attention to the physiological significance of the glands that had been described as existing near the thyroid gland by Sandström in 1880. Meanwhile they had been almost forgotten. He stated that when the thyroid gland and the parathyroid glands are simultaneously extirpated in rabbits, the animals react with tetany, whereas when the thyroid gland alone is removed, tetany does not occur. He expressed the opinion that the parathyroid glands must stand in some peculiar relation to tetany, and suggested that perhaps these glands can hypertrophy and take over certain of the functions of the thyroid gland. Gley was handi-

capped to a certain extent by the imperfect knowledge, then existent, regarding the anatomical relations of the parathyroid glands and of the thyroid gland in the rabbit. Five years later, Kohn made a very accurate study of the region of the thyroid gland in the cat and in the rabbit, and added two parathyroid glands to the two that Gley had earlier recognized in the latter animal, thus making more exact experimental investigation of the region possible.

The next great advance in knowledge was to come from Italy. In 1896-7, Vassale and Generali (*a*)(*b*) applied to man Gley's idea of the relation of the parathyroid glands to tetany in animals. At a meeting of the medical and surgical society in Modena, these Italian investigators made the following interesting statement: "If, in man, the parathyroid glands are removed during thyroidectomy, tetany may appear; if they are not removed with the thyroid, then cachexia strumipriva or myxedema may appear." In this very year, 1897, and in the preceding year, 1896, the best monographs (*vide infra*) that had been written on tetany up to that time (respectively that of L. von Frankl-Hochwart of Vienna, and that of B. Oddo of Marseilles) were published, and though, in them the clinical phenomena of the disease and its history are so admirably described that these monographs must be permanently used as sources, still they contain not a single reference to the parathyroid glands or to their possible relations to tetany. That such a fundamental observation as that made by Gley in 1890 could, for so long a period as seven years, be thus overlooked is astonishing. But 'tetania strumipriva' had come to be so generally regarded as a "tetania thyropriva" by both surgeons and clinicians that even the report of Vassale and Generali in 1897 passed almost unnoticed. Indeed, as late as 1901, von Eiselsberg, who afterwards became one of the strongest supporters of the parathyrogenous doctrine of tetany, when commenting upon Vassale and Generali's view that the functional disturbance of tetany is due to loss of function of the small parathyroid glands rather than to that of the large thyroid gland, remarked *"das ist von vornherein nicht wahrscheinlich."* I shall mention a little later the further observations, experiments and inferences that have led to a general acceptance of the doctrine that tetany, at least in many of its forms, depends upon loss of, or insufficiency of, function of the parathyroid glands.

In tetany, as in other subjects in clinical medicine, progress has been furthered, not alone by investigators that have made original observations and experiments and have recorded their results, but also by those physicians that from time to time have taken stock, as it were, of the knowledge existent, and presented it to the profession in organized form. The ability thus to organize knowledge and prepare it for general diffusion is second in value only to the ability to conduct fruitful original research. That ability in its highest form presupposes a mind of great

compass and comprehensiveness, the power to weld widely divergent materials into a homogeneous and symmetrical unity, the faculty of seeing to the heart of things through masses of accessory details, as well as deftness in the use of language, a feeling for accuracy and for fairness in the distribution of credit, a broad training not only in the clinical but also in the preclinical medical sciences, and, finally, a calmness and sagacity of judgment that will ensure caution and temperance in the consideration of matters concerning which there is still clash of opinion. We owe to the writers of good textbooks and of comprehensive monographs, therefore, a debt that is not always fully recognized, for such writers are the preparers of paths that often lead quickly to the discovery of new knowledge. Two publications of this kind on tetany that appeared near the end of the nineteenth century deserve especial mention, (1) that of B. Oddo of Marseilles (1896), and (2) that of L. von Frankl-Hochwart of Vienna (1897). I have already referred to them above. In both of these monographs we meet with a breadth of treatment and a mastery over materials that have placed students of tetany under a debt of gratitude to the authors hard to overestimate.

One of the important contributions made by von Frankl-Hochwart in his monograph was his classification of the tetany of adults from the etiological standpoint. He subdivided tetany into (1) the tetany that occurs in otherwise healthy individuals (idiopathic tetany, epidemic-endemic tetany, tetany of workmen), (2) tetany in gastric and intestinal diseases, (3) tetany in acute infectious diseases, (4) tetany after intoxications, (5) tetany in maternity (pregnancy, parturition, lactation), (6) tetany after operations for goiter, and (7) tetany associated with certain nervous diseases. His descriptions of these seven forms of tetany and of the tetany that occurs in children are to-day most valuable for reference, and I have drawn much upon them, as well as upon B. Oddo's descriptions, in the preparation of the present article.

Since the appearance of Oddo's exhaustive review and of von Frankl-Hochwart's elaborate monograph, the interest of the internists and of the experimental workers who have studied tetany has centered in the problem of the etiology and pathogenesis of the disease with especial reference to the parathyroid glands on the one hand, and to mineral and intermediary metabolism on the other; and coincident with these studies of etiology and pathogenesis, much progress has been made through clinical observations and animal experiments in the search for successful methods of diagnosing and treating tetany and parathyroid insufficiency.

After the publication of Vassale and Generali's papers, surgeons, physiologists and pathologists began actively to busy themselves with experiments upon thyroidectomy (with, and without, parathyroidectomy) in animals. A consensus of opinion was gradually arrived at. Removal

of the thyroid gland alone causes myxedema without tetany (*myxedema operativum chronicum, cachexia strumipriva*). Removal of three or more parathyroid glands alone causes tetany without myxedema (*tetania parathyropriva*). Removal of both thyroid gland and parathyroid glands simultaneously causes tetany with myxedema (*tetania thyroparathyropriva; myxedema operativum acutum*). Tetany was found to follow experimental parathyroidectomy in dogs, cats, rabbits, rats, mice, goats, monkeys, hens and frogs. Animals with partial parathyroidectomy often remained free from symptoms, but could be shown to be in a condition of latent tetany, and Vassale showed that animals with such latent tetany might exhibit manifest tetany during pregnancy. Practically all of the symptoms observable in acute and chronic tetany in man have been reproduced in animals by removal of, or injury to, their parathyroid glands. In these experimental contributions a host of investigators have been active (Gley (*c*)(*e*), Vassale and Generali (*a*)(*b*), Erdheim, Moussu, Christiani, W. S. Halsted, W. G. MacCallum, Victor Horsley, Laurence Hermann, A. J. Carlson, A. Biedl, and many others).

Considering the observations made by those who experimented upon animals, there remained but little room for doubt that tetany after strumectomy in human beings, too, must be due to removal of, or injury to, the parathyroid glands. This view had been put forward by Jeandelize (1902) and by Biedl, and was strongly supported by the studies of Pineles (*b*)(1905), Benjamin (1902), and Erdheim (*c*)(1906). Thus, Pineles showed that in the clinical picture of thyro-aplasia, in which there is complete absence of the thyroid gland, when the parathyroid glands are entirely normal, signs of tetany are never present. He argued that this demonstrated a definite connection between tetany and the loss of function of the parathyroid glands. He adduced, further, the observations, (1) that tetany does not follow extirpation of goiter of the lobulus lingualis (*Zungenkropf*), whereas (2) tetany relatively often appears when strumectomy is done without removing the isthmus of the thyroid. These two facts also demonstrated the existence of a close connection between the parathyroid glands and the contractures of tetany, for the four parathyroid glands lie behind the lateral lobes of the thyroid and there are no parathyroids behind the isthmus or the lobulus lingualis when the latter is present. Even more conclusive were the observations of Benjamin and of Erdheim. Thus, Benjamin found that from one to three parathyroid glands were sometimes attached to extirpated human goiters, involving a loss of parathyroid function sufficient to explain the postoperative tetany; and Erdheim showed that, in three cases of tetany that followed partial strumectomy, all four parathyroid glands had been removed with the parts of the thyroid that had been taken out. In one instance Erdheim found at autopsy a parathyroid gland that had undergone necrosis as the result of cutting off its blood supply at the operation for goiter. These clinical-pathological

examinations demonstrated, then, beyond any reasonable doubt, that tetany after strumectomy is due to removal of, or injury to, the parathyroid glands, in other words that in tetania strumipriva the human being is in a *status parathyroprivus* (Halsted (*a*)).

The result of all these studies was that the technic of the operation of strumectomy could be rationally revolutionized, so as to avoid injury to, or removal of, the parathyroid glands and an ensuing tetany. Surgeons learned how to leave the parathyroid glands behind, how to avoid injury to them, and how to preserve their blood supply intact when operating upon goiter. As so often happens in medicine, however, an approach to what afterwards was conducted as a rational procedure had already been gained on empirical grounds by astute and observant surgeons before the reasons for it could be known. Thus, Austrian surgeons had noticed that tetany was less common when the thyroid gland was resected at operations for goiter than when one or both lateral lobes were extirpated.

Chronic tetany was produced experimentally in dogs as far back as 1888. In that year W. S. Halsted had been puzzled by the development of chronic tetany in animals in which he had ligated all the vessels, both veins and arteries, of both lobes of the thyroid, with the exception of the superior thyroid artery and the inferior thyroid vein. These dogs suffered from chronic tetany and ultimately died, notwithstanding the fact that the thyroid lobe enlarged after the operation and microscopically showed a picture of hypertrophy. "Dogs so treated lived nearly three months on the average, in contrast to those with thyroid extirpation, which died usually in from two to nineteen days after operation." These first recorded cases of chronic experimental tetany were probably due, as Halsted himself suggests, to the cutting off of the circulation of both superior parathyroids, by the ligature of the superior veins, and by the handling incident to the ligation. The two internal parathyroids probably survived in these dogs as well as the hypertrophied thyroid, for, if no parathyroid tissue had remained, the dogs could not have lived for three months, as they usually did; they would have died within three weeks of the acute and total abolition of the parathyroid function.

That several of the forms of tetany other than tetania strumipriva are also due to lack of parathyroid function is strongly suggested by the identity of the clinical phenomena in these forms. It seemed highly improbable, Pineles urged, that this identity could be accounted for otherwise than by the assumption of a common pathological-physiological basis of hypoparathyroidism (*unitary conception of the pathogenesis of tetany*). Studies of etiology later than those of Pineles suggest that the unity of pathogenesis may lie in metabolic conditions (some of them parathyrogenous, some of them non-parathyrogenous) that cause the peculiar hyperexcitability of the nervous system.

The recognition that postoperative tetany is due to loss of para-

thyroid function stimulated attempts at restoration of this function by (1) *substitution therapy* (administration of parathyroidin by Vassale; exhibition of beeves' parathyroid glands by Halsted and MacCallum; hypodermic injections of parathyroidnucleoproteid by Beebe), and (2) *transplantation of parathyroid glands* in animals after parathyroidectomy (Biedl, Pfeiffer and Meyer, Halsted (*a*)(*b*)(*c*)(*d*), Landois (*b*), Joannovics, and many others), and, later, in man in tetany after strumectomy (von Eiselsberg, Pool, Böse and Lorenz, Danielsen, Krabbel, and others). The difficulties encountered and the results thus far obtained will be referred to when the treatment of tetany is described (*vide infra*).

Following upon the studies of Sabbatani, of Jacques Loeb, and of J. B. MacCallum on the physical significance of certain kations, and especially of calcium ions in depressing neuromuscular excitability, interest was aroused in the mineral metabolism in tetany. Quest, Netter, Underhill, MacCallum and Voegtlin, Stöltzner (*a*), Cooke (*b*), Cybulski, Ott and Scott, Howland and Marriott, Hoskins and Gerstenberger, Binger, Grant and Goldman, and others, have studied the subject and have reported somewhat conflicting results. Three facts, however, appear to have been established:—(1) in tetany, the blood and tissues often become deficient in calcium; (2) the administration of calcium salts will often exert an ameliorative effect upon the symptoms of tetany; and (3) the acid-base equilibrium in the body may be disturbed, either in the direction of an acidosis, or of an alkalosis.

Recently, researches in intermediary and end metabolism have been undertaken with the hope of throwing light upon a hypothetical tetany toxin, some seeking through it to support the old theory of auto-intoxication from the gastro-intestinal tract (Bouveret); others looking for an intoxication due to disturbances of the acid-base equilibrium (Moussu (*c*), Binger, Grant and Goldman) or to disturbances of the kation equilibrium in the body (MacCallum and Voegtlin); others suspecting the cause of tetany to lie in a thymus intoxication (Uhlenhuth (*a*)); and still others identifying the cause with an accumulation of guanidin or guanidin derivatives in the blood and tissues (W. B. Koch (*a*) (*b*), D. Paton (*c*) and collaborators). That, in the last analysis, the parathyroid insufficiency of tetania parathyropriva may prove to be an insufficiency of certain specific ferments is another hypothesis now looming above the horizon (Beebe, Rowe, Barker).

Very recently (1920) evidence has been brought by Collip and Backus of Canada and by Grant and Goldman of St. Louis that tetany can be experimentally produced in human beings by forced respiration, and that this tetany is associated with a definite alkalosis.

Several of the more recent collective reviews of the literature of special phases of tetany and of the subject as a whole may be mentioned in concluding these historical notes. Among the former, I would refer

the reader to a review of the diagnosis and therapy of tetany by Chvostek (*d*), junior (1909); to that of the myotonic symptoms of tetany by von Orzechowski (1909); to that of the relations of tetany to epilepsy by Redlich (1911); and to that of the autonomic phenomena of tetany by Falta and Kahn (1911). Of the general reviews of the subject of tetany, in addition to the older monographs of Oddo and of von Frankl-Hochwart, may be cited that of Risien Russell in *Allbutt's System,* that of Phleps in Lewandowsky's *Handbuch der Neurologie,* that of Eppinger in Kraus and Brugsch's *Spezielle Pathologie und Therapie,* and, especially, that of Biedl in the last edition of his *Innere Sekretion.*

III. Symptomatology of Tetany

By far the majority of the symptoms and signs in tetany are referable to a hyperexcitability of the nervous system. This hyperexcitability involves the motor apparatus, the sensory apparatus, and the autonomic apparatus. When the hyperexcitability is of high grade, intermittent attacks of spontaneous tonic contractions of muscles occur (*manifest tetany*). When the hyperexcitability is somewhat less marked (*latent tetany*), there are no attacks of spontaneous tonic contractions, but the evidences of hyperexcitability can be easily elicited by means of special tests. The so-called 'tetanoid' states are also to be regarded as examples of latent tetany and are sometimes described as the *formes frustes* of tetany.

1. The Tonic Contractions of the Muscles in Manifest Tetany

The tonic contractions of the muscles that appear spontaneously in (manifest) tetany have been observed by all physicians of large experience, and have, long since, been very accurately described. The French physicians, especially, in their early studies of tetany, made careful analyses of the muscular spasms in tetany and of the pathological attitudes of the different parts of the body that result from them. This is a form of observation and description in which French clinicians are known particularly to excel.

In adults the tonic spasms of the musculature in manifest tetany occur most frequently in the upper extremities, less frequently in the lower extremities, and less frequently still in the muscles of the head, neck and trunk. In children it is common to have the upper and lower extremities simultaneously involved in the muscular spasms of tetany. In both adults and children the hyperkinesis of tetany occasionally may be so marked as to constitute a general convulsion.

In the classical form of tetany, the attitude assumed in the attack

of tonic contractions by the upper extremities, so well described by Trousseau, is very characteristic. The fingers are held straight, or nearly straight, and a little flexed at the metacarpophalangeal joints. The four fingers are crowded together by adduction, so as to form a cone. The thumb, too, is strongly adducted and opposed, often so much so as to be turned into the cavity formed by the adduction of the other fingers, or into the palm. Even the metacarpal bones are somewhat adducted, so that the dorsum of the hand presents a convex surface and the palm becomes scarcely visible. The whole effect is that of a cone-shaped, or pyriform, hand. It is the shape of hand assumed by the obstetrician when he goes to pass his hand through the vagina into the cervix of the

Fig. 1. Typical position of the hand in an attack of tetany. This is the so-called "obstetrical hand." The same appearance, due to pressure upon the upper arm, is known as Trousseau's phenomenon. (After E. Phleps, in Lewandowsky's "Handb. d. Neurol.," published by J. Springer, Berlin.)

uterus in the parturient woman; hence the name "obstetrical hand," or *main de l'accoucheur,* given to it by Trousseau (Fig. 1).

Other attitudes of the hand are met with in tetany, but they are less common. Thus, sometimes, the thumb, instead of being opposed and markedly adducted, so as to be turned into the palm, is extended, so as to remain in line with the four fingers, the hand as a whole being in the position adopted when one presses the hand flat upon a sheet of paper; hence the French term for this attitude, *main en presse papier.* In other instances the fingers may be flexed at all their joints through spasm of the long flexor muscles; the fist is then tightly closed and the contracture may be so marked that the finger nails are driven into the skin, so as to cause necrosis (*main de l'hemiplégique contracture*). In still other instances a bird claw position (*main en griffe*) of the hand is assumed, due to spasm chiefly in the interossei and lumbricales (Fig. 2). In certain rare examples of tetany spasm the fingers may even be spread

wide apart and fully extended at all joints. As Oddo has emphasized, it is well to be familiar with these different varieties of attitude that the hand may assume, in order that errors in diagnosis may be avoided.

At the wrist joint the hand is slightly flexed, as a rule, upon the forearm. In rare instances there may be extreme flexion at the wrist, so that the hand and the forearm form a right angle (*main botte*).

Fig. 2 Tetania persistens (9 months old child); hands and feet in typical claw position. (After J. Ibrahim, in Feer's Lehrbuch der Kinderheilkunde, Jena, 1912.)

The forearm itself generally occupies a position intermediate between pronation and supination.

About the elbow and the shoulder there is, as a rule, no contracture of the muscles, though sometimes these muscles are also involved, in which event the elbow is flexed and the forearm is pronated and folded across the chest, while the upper arm is held in adduction close to the side of the body.

The lower extremities, less often affected in adults, are quite commonly involved in children. When the cramps involve these parts (pedal spasm), there is marked plantar flexion of the feet, while the sole of the foot is turned medialward (position of talipes equinovarus). This plantar flexion at the ankle joint is due to spasm of the M. gastrocnemius and the M. soleus, innervated by the N. tibialis, whereas the supination of the foot, that is to say its adduction with elevation of its medial margin, is due to contraction of the M. tibialis posticus, innervated also by the N. tibialis. The dorsum of the foot becomes convex, and the sole of the foot concave, due to strong adduction of the metatarsal bones, consequent upon contraction of the Mm. interossei volares, which are innervated by the N. tibialis. The toes, too, are strongly flexed and adducted, owing to contraction of the Mm. interossei and the lumbricales. The great toe, too, is usually strongly adducted (M. adductor hallucis), sometimes so

strongly as to be turned in under the other toes, much as the thumb is turned into the palm of the hand. In children this attitude of the foot is very much like that of a ballet dancer, walking on her toes (*démarche des danseuses*). Less commonly a valgus position of the foot is assumed (spasm of the Mm. peronei), or the foot may be held rigidly in a fairly normal position. It is, however, a striking fact that the contractions in the lower extremity predominantly concern, as a rule, the muscles innervated by the N. tibialis, just as those in the upper extremity predominantly concern the muscles innervated by the N. ulnaris.

The knees are generally held in rigid extension when the lower extremities are involved; rarely, they are flexed. In the former instance, the spasm is in the M. quadriceps femoris; in the latter, more rare, it is in the flexor muscles at the back of the thigh. There may also be contracture of the adductors of the thighs, so that the limbs are held close together, or the thighs may even be crossed (scissors position). Occasionally the thighs are flexed at the hips (spasm of the M. iliacus and the M. psoas), but this attitude is rare.

It is interesting to note that, both in the lower and the upper extremities, the contractures in tetany are more marked distalwards and less marked proximalwards. Thus, in the upper extremities, the shoulders and elbows are often free, whereas the wrist, hand and digits are held rigid; and, in the lower extremities, the hip joints are much less often affected than are the knees, ankles and toes. The greatest rigidity seems to be in the small muscles of the hand and of the foot; that is, as has above been pointed out, in the distribution of the N. ulnaris in the upper extremity and in the distribution of the N. tibialis in the lower extremity.

In an analysis of 122 cases, v. Frankl-Hochwart (*a*) (*b*) observed muscle spasm in the lower extremities in 70 instances. Spasmodic contractures in the feet (*pedal spasms*) occur but rarely alone, but are nearly always associated with spasms in the hands and arms (*carpal spasms*), the combined attitudes thus forming the well known *carpopedal spasms* of tetany.

In the trunk, the thoracic muscles are sometimes involved in the spasms of tetany, especially the M. pectoralis major and the M. trapezius. Even the abdominal muscles may be concerned in the contractures, the Mm. recti standing out sometimes like stiff bands under the skin on the front of the abdomen. Danger of asphyxia may arise, if the diaphragm undergo spasm along with spasm of the respiratory muscles of the trunk and abdomen.

The whole trunk may be hyperextended (*opisthotonos*), as in tetanus, due to spasm of the Mm. ileocostales dorsi et lumborum; less often it is in flexion (*emprosthotonos*); still more rarely, it is observed in lateral flexion, due to spasm of the M. quadratus lumborum.

When the muscles of the neck are involved, the head is usually drawn backward, and the neck more or less excavated, owing to spasm of the

M. splenius capitis et cervicis of each side. An attitude of *torticollis* appears when the contracture involves predominantly the M. sternocleidomastoideus and the obliquus capitis inferior of one side.

In the face, *trismus* may appear, owing to spasm of the M. masseter on each side. Sometimes all the muscles of the face are rigid and immobile, yielding the so-called *"tetany face."* If the M. orbicularis be especially involved, the lips may be pointed. A fish mouth attitude (*carp mouth*) has been described by some observers, due probably to drawing of the angles of the mouth downward by spasm in the Mm. quadrati labii inferioris.

The characteristics of the *tetany face* are worthy of detailed description. Since carpopedal spasms, so characteristic of the manifest tetany of adults, are often absent in the tetany of children, any criterion that will help in the early recognition of infantile tetany must be gratefully welcomed. Uffenheimer (1905), of Münich, drew attention to the fact that a large number of children, suffering from tetany, exhibit a peculiar facial expression, which deviates extraordinarily from that of normal healthy children of the same age. The specific childlike features of the face disappear and in their place one observes an expression of "reflection" or of "care" (Fig. 3). Uffenheimer, speaking of this to his colleagues, described the facial expression as *knifflichen verschlagenen.* This peculiar change in the facial expression depends on the fact that the muscles of the face are under a certain degree of tension. There exists, in other words, the very slightest state of tonic spasm of the facial muscles. It is the smallest expression of that tonic spasm that we have learned to recognize in true tetanus as "risus sardonicus," due to permanent spasm of the mimic musculature. Finkelstein (*a*) had earlier pointed out, in his textbook on the diseases of sucklings, that participation of the face in the rigidity of tetany produces a peculiar stiffness with permanent contraction of the M. corrugator or of the M. orbicularis oris (carp mouth). And Escherich (*b*), in 1903, had observed an irritable frightened behavior of the children, with an anxious expression and an increased tonus of the musculature of the face. But Uffenheimer emphasized the increased tonus and a reflective, careworn look, rather than an anxious expression. On analysis, the muscles concerned in the slight spasm that gives rise to the tetany face are all innervated by the N. facialis. In the first place, the M. orbicularis oris (pointing the lips), the M. zygomaticus and the M. quadrati labii inferioris (drawing the angles of the mouth to the side and downward) participate in the spasm. Their contractures together give the reflective look to the face, and this is strengthened by the wrinkling of the forehead transversely and the elevation of the eyebrows (due to slight spasm of the M. epicranius), and especially by the slight frowning, or longitudinal wrinkling on both sides of the root of the nose, due mainly to contraction of the M. corrugator on

each side. Uffenheimer stresses the fact that this tetany face appears very early in children and is therefore of great value for early diagnosis. It is to be regarded as a premonitory symptom, though why this slight tonic spasm of the facial musculature should appear at so early a stage

Fig. 3. The tetany face in children. (After Uffenheimer, Jahrb. f. Kinderheilk., 1905.)

in the disease is not clear. Sometimes the features of the tetany face become more marked when the child is crying than when it is at rest; or the tetany face may first appear during an eclamptic attack. Though this tetany face is not present in all cases of tetany in children, it is so

often present before other signs of the disease are recognizable that it should always be looked for by the pediatrist, and, if found, the galvanic excitability of the motor nerves should at once be measured.

The eye muscles are sometimes the site of spasm in manifest tetany. A whole series of different involvements of the eye muscles, influencing the movements of the upper lids and of the eyeballs, has been described by Oddo (1896) and by Kunn (1897). Even the intrinsic muscles of the eye are occasionally concerned (accommodation spasm; pupillary changes). Strabismus, nystagmus, and conjugate deviation have all been noticed in different instances in tetany.

Spasm of the muscles of the tongue and of the pharynx may interfere with swallowing and with speech in adults, or with suckling in children. Apparently involvement of the muscles of the face and trunk is more common in the child than in the adult.

Spasm of the laryngeal muscles *(laryngospasm)* is a common symptom in infantile tetany, and one by no means devoid of danger to the life of the child.

Limitation of the spasm to single muscles, or to single muscle groups in various parts of the body, has been described by several authors.

The *smooth muscle* innervated by the autonomic nervous system (sympathetic and craniosacral) is probably more often involved in the spasms of tetany than is usually believed. Thus, besides the spasm of the sphincter and the dilator of the iris and of the ciliary muscle above referred to, spasms have been observed in the esophagus (*esophagismus*); in the stomach (*gastrospasm*); in the intestines (*enterospasm*); in the sphincter and detrusor of the urinary bladder, causing, in the one instance, *urinary retention,* in the other, *enuresis;* and in the smooth muscle of the bronchi, causing *asthmatic attacks.* Even *spasm of the heart muscle,* due to tetany, has been described by Ibrahim (*a*) (1911). During the present year I saw with Dr. Sydney Miller a patient who suffered from postoperative tetany, and who died suddenly in the night with a severe pain referred to the left shoulder. As the patient had also a moderate grade of chronic arterial hypertension, we thought of death from angina pectoris, though death from spasm of the heart due to tetany had also to be considered as a possibility.

Spontaneous attacks of muscular spasm in manifest tetany are usually *bilaterally symmetrical* in the extremities, as has already been stated. Cases of *hemitetany* do, however, occur, though they are rare. Von Frankl-Hochwart described two such cases. In one of them the extremities on the right side entered into the contracture positions, whereas those on the left side remained free from spasm; on one occasion, however, the patient stated that he had noticed, simultaneously, paresthesias in the left hand. Von Jaksch has also described a case of tetany, in which the spasms affected only the left upper and lower extremities. In Fig. 4 I have

reproduced an illustration of a case of hemitetany described by Curschmann in 1910. In this figure the limitation of the spasm to the extremities of one side is clearly visible.

The *duration of the attacks* varies much, even in the same individual and at any given period of the disease. Thus, the tonic rigidity may last only a few minutes, say fifteen; but in the majority of instances the attacks last from one half hour to three hours. Hoffmann (*a*) (*b*) has described a case in which the attack of tonic contracture lasted as long as ten days.

Fig. 4. Severe attacks of hemitetany of the left arm with involvement of the shoulder musculature. The patient is trying, as usual, to stop the painful cramps with his right hand. The left leg is only a little involved. Note the elevation of the knee. (After H. Curschmann, in Deutsches Zeitschr. für Nervenheilkunde, 1910.)

The *exciting cause* of the actual attack seems to differ in different cases. Sometimes it appears to be emotional excitement; sometimes, a slight trauma; sometimes, exposure to cold, for example, towards morning in bed; in a few instances the spasms seem to be of the intention type, as in Thomsen's disease.

The exquisitely tonic character of the contractions is very characteristic of tetany. Occasionally, however, outspoken clonic contractions are met with, and sometimes *fibrillary twitchings* and *tremor*.

Following the seizures, the muscles affected may be markedly paretic; sometimes, indeed, *paresis* seems to occur as an equivalent of a tetany attack, not only in human beings, but in experimental animals. The paresis of muscles is most often noticeable in the lower extremities. Especially when the patients walk, they exhibit a slow, shuffling, often waddling gait, suggestive of muscular dystrophy.

Observation has also been directed toward the *time of day* in which contractures appear. Attacks of muscular spasm, it would seem, may occur at any time in the twenty-four hours. According to von Frankl-Hochwart's analysis, they occur quite irregularly in some patients; in others there is a predilection for the afternoon, in still others, for the night. Occasionally, a certain type of contracture occurs at certain hours.

The *prognosis of the single attack* of muscle spasm *quoad vitam* is good. Now and then a patient dies in an attack, though this is very rare.

If death occur, the tonic spasm of the muscles may persist until post-mortem rigidity sets in.

2. The Increased Mechanical Excitability of the Motor Nerves in Tetany

In nearly all cases of tetany, both manifest and latent, there is *increased mechanical excitability of the motor nerves,* whether the stimulus be compression by a ligature (Trousseau phenomenon), tapping on a peripheral nerve trunk (Chvostek's phenomenon), or making tension on the large nerves innervating an extremity (arm and leg phenomena of Ferenczi, Pool, and Schlesinger (*a*) (*b*)).

Trousseau's Phenomenon

Trousseau, in 1864, pointed out that if, in the intervals between attacks of manifest tetany, a ligature be applied firmly about the upper arm so as to suppress the flow of blood through the brachial artery, the typical attitude of obstetrical hand can be produced within a few minutes. The more severe the tetany, the quicker will the abnormal attitude be assumed after the ligature is applied. When the nerves are very hypersensitive to mechanical stimuli, firm pressure with a finger in the bicipital groove will call forth such an attack of spasm. The sign, described by Trousseau, is exceedingly characteristic and has been regarded by many as pathognomonic of tetany. The test is a very simple one to apply, and it should always be performed, if the existence of tetany be suspected. Even in latent tetany the Trousseau phenomenon will usually appear, if pressure be exerted on the nerves of the upper arm.

In performing the test, one may apply an Esmarch bandage at the middle of the upper arm, making the pressure strong enough to interrupt the arterial flow. I myself prefer to make use of the cuff of the ordinary blood pressure apparatus, since it is practically always in one's consultation bag. One puts on the cuff, raises the pressure in the manometer to about 200 millimeters of mercury, and waits for at least five minutes, in case the contracture does not earlier occur. The obstetrical hand attitude will as a rule become evident in tetany in from two to three minutes after the pressure is applied. In a case of postoperative tetany, which I recently had opportunity to observe, the surgeon told me that he had made pressure in the bicipital groove, but that Trousseau's phenomenon had not appeared. On applying the blood pressure cuff, the typical obstetrical hand became evident in about three minutes. The surgeon then stated that he had not kept up the pressure quite so long. This matter of the time required to elicit the sign should be kept in mind. If

one suspect tetany at all, it is well to keep the pressure applied for at least five minutes before admitting that the Trousseau phenomenon cannot be made manifest. Clinicians were earlier exercised to decide whether the pressure that elicits the Trousseau phenomenon acts through mechanically stimulating the nerves or through cutting off the blood supply. Von Frankl-Hochwart's experiment bearing upon this point seems to me conclusive. He found in experimental tetany in the dog that the slightest pressure applied to the exposed nerve sufficed to set free the contracture, whereas the strongest pressure upon blood vessels alone remained without effect.

The gradual appearance of the contracture when the Trousseau phenomenon is elicited is another point that I should like to emphasize. One sees the fingers begin to straighten out and to become adducted, and the thumb is gradually opposed and adducted and slowly turned into the palm. The Trousseau phenomenon, as it develops, is a most interesting clinical sign to watch.

A *pseudo Trousseau phenomenon* has been described as occurring in hysteria. But if one be familiar with the true Trousseau phenomenon and its gradual appearance, he will rarely be deceived by the simulation of a hysterical. I should advise caution, too, before assuming that a contracture resembling a Trousseau phenomenon is due to hysteria rather than to tetany, even in a patient known to be hysterical, for hysteria and tetany may occur together in the same person.

Though tetany may exist in persons in whom the Trousseau phenomenon cannot be elicited, nevertheless it is positive in so large a proportion of cases that it is a sign exceedingly valuable to the diagnostician. Von Frankl-Hochwart has estimated that the Trousseau phenomenon is positive in two thirds or three fourths of all cases of tetany, manifest and latent.

Though all are now agreed that the pressure applied to call forth the Trousseau phenomenon is effective through stimulating the nerve rather than through cutting off the blood supply, it is still undecided whether the Trousseau phenomenon is a response due to direct stimulation of the hyperexcitable motor nerves, or whether it is a reflex phenomenon, that is, one in which the motor response is produced indirectly by stimulation of the sensory nerves. Schlesinger, a careful Viennese observer, has strongly championed the latter view. He argues that the Trousseau phenomenon can scarcely be due directly to mechanical stimulation of the hyperexcitable motor nerves, since response to mechanical excitation is most marked in the facial nerve, and compression of that nerve in the face does not lead to tonic spasm. Furthermore, the Trousseau phenomenon is most marked in the arms, where the nerves are only moderately mechanically excitable, and even when mechanical hyperexcitability in a given person is very distinct in the arm nerves it may not be possible

to elicit the Trousseau phenomenon. Schlesinger also adduces the observation that patients who show a high grade of galvanic excitability of the motor nerves need not necessarily exhibit the Trousseau phenomenon, and the same is true also of the Hoffmann sign. In other words, there is no constant coincidence of the Trousseau phenomenon with either Erb's phenomenon or Hoffmann's. Another important point that may be mentioned in this connection is the fact that pressure applied to one arm, to produce the Trousseau phenomenon in that arm, may occasionally call forth the Trousseau phenomenon also in the opposite arm; the contraction in the latter must necessarily be of reflex origin. In any case, the hyperexcitability that is responsible for the Trousseau phenomenon must, on account of the uniformity of the contracture that occurs, correspond to some definitely circumscribed neural mechanism. Neurologists and experimental pharmacologists have done many experiments with the object of determining the localization of the tetany poison in the nervous structure (*vide infra*), but thus far the progress made in this direction has been very limited.

Tonic spasms in the lower extremities, also, can sometimes be elicited in tetany by applying a ligature or a cuff around the thigh, so as to compress the underlying structures. The result is, however, less frequently positive than in the upper extremities.

It must not be forgotten that the Trousseau phenomenon may be entirely absent in undoubted cases of tetany. No diagnostician is justified, therefore, in excluding tetany merely by demonstrating the absence of the Trousseau phenomenon.

Chvostek's Sign

(*The Facial Phenomenon; The Sign of Weiss*)

In tetany the mechanical excitability of the motor nerves is markedly increased, a fact that was discovered by the senior Chvostek (1878). Though this hyperexcitability probably exists in all motor domains, it is especially easy to demonstrate, as Chvostek pointed out, by tapping the motor nerves of the face with a small percussion hammer or its handle, or with the tip of the finger. When the mechanical hyperexcitability of the nervus facialis is very pronounced, the mere stroking of the area of skin over the nerve by the tip of the finger will call forth lively contractions in the muscles innervated by it.

According to the degree of hyperexcitability found to exist, *three grades of the facial phenomenon* are distinguishable. Thus, in the highest grade (*Chvostek I*) a tap in the region of the pes anserinus in front of the ear will cause the muscles of the whole side of the face (muscles of the forehead, eyelids, cheeks, nose, and lips) suddenly to contract. This

highest grade of mechanical excitability is somewhat rare. It is much more common to meet with the second grade (*Chvostek II*), in which movement of the nostrils (M. nasalis), and a drawing of the angle of the mouth to the side (M. quadratus labii superioris) follow tapping upon a spot beneath the zygoma. The third grade of positive reaction (*Chvostek III*), indicating a still lower degree of mechanical excitability of the facial nerve, is manifested as a slight twitch at the angle of the mouth when the same region is tapped.

This facial phenomenon, or Chvostek's sign, is certainly very valuable for quickly yielding a clew to the possible existence of tetany, since it can be performed on a suspect in a moment or two. It is, however, sometimes absent in true tetany, and it may be positive in cases in which there is no other reason for assuming the existence of tetany (psychoneurotic states, tuberculosis, Graves' disease, etc.). It appears to be more constantly present in the tetany of adults than in that of children (Schlesinger), and to be more frequently met with in chronic than in acute tetany (von Frankl-Hochwart). According to Weiss, it may sometimes be positive in normal persons. During epidemics of tetany in Vienna, von Frankl-Hochwart could often demonstrate the presence of Chvostek's sign in apparently healthy people, but admitted that this might mean the existence in such persons of *formes frustes* of tetany.

It seems certain that Chvostek's sign depends upon a direct mechanical hyperexcitability of the facial nerve, and not upon an abnormal reflex activity. The arguments *pro* and *con* have been marshaled by von Frankl-Hochwart.

In sucklings, one can sometimes elicit, instead of a typical Chvostek sign, a lightning-like contraction in the orbicularis oris muscle simply by gently tapping the lips of the infant with a percussion hammer.

Another sign that is doubtless due to mechanical hyperexcitability of the motor nerves is F. Schultze's (*b*) *tongue dimple sign*. The patient is asked to protrude the tongue, and the observer taps it lightly with the percussion hammer. At the site of application of the mechanical stimulus, a depression or dimple appears. The same sign is sometimes met with also in myotonia congenita (Thomsen's disease).

Increased idiomuscular excitability is sometimes demonstrable in tetany. One tests for it by tapping the surface of a muscle, say the pectoralis major, with a percussion hammer, and compares the response elicited with that obtainable in normal persons.

The Arm and Leg Phenomena of Tetany

In 1906 E. H. Pool (*a*) of New York, studying a case of postoperative tetany through a long period at the French Hospital, observed the constant response of contracture of the muscles of the upper extremity upon

forcible abduction of the arm and of contracture of the muscles of the lower extremity upon forcible flexion, at the thigh, of the lower extremity extended at the knee. In the report of this case in the *Annals of Surgery* for October, 1907, these interesting "arm and leg phenomena" of tetany were referred to as follows: "Contractures also resulted from making the sciatic nerve tense by holding the patient in the sitting position, so that the trunk and thighs were flexed beyond a right angle, with the legs extended; or by putting the nerves of the brachial plexus on the stretch by elevating the arm above the head with the forearm extended (extreme abduction). The contracted muscles were always board-like to the touch." The methods of evoking these contractures in the extremities were, in his paper, illustrated by reproductions of photographs (Fig. 5

Fig. 5. Method of producing tetanic spasm of the hand by stretching the brachial plexus by means of forcible abduction of arm. (The Arm Phenomenon of Pool.) (After E. H. Pool, Annals of Surgery, 1907.)

and Fig. 6). Pool gave a further description of the details of his observations of the leg and arm phenomena in tetany in another paper published in 1910, stating that, "in the arm test the abduction must be as extreme as possible, the elbow being held in full extension; the brachial plexus is thus put upon the stretch. The hand took, as a rule, a position similar to that produced by stimulation of the ulnar nerve, with at times flexion of the wrist," and that in the leg test "the muscles of the calves become markedly contracted and the feet assume a position of extreme plantar flexion, with the toes usually turned forcibly toward the soles." About one and one half minutes elapse after the test is applied before the response is seen, though the time is variable on applying the test on

different occasions. The response, as described in Pool's patient, gradually grew less marked and finally disappeared after about twelve months observation. The positive response for these arm and leg phenomena seemed to run parallel with the positive response of Trousseau's sign as well as with the response of Chvostek's sign. Pool stated, in his first report of the case, that "the value of the two tests, dependent upon stretching the nerves of the brachial plexus and the sciatic nerve, which were so striking in our case, cannot be estimated until repeated trials have been made in other cases." He considered the tests of value as "an ad-

Fig. 6. Method of producing tetanic spasm in the feet by stretching the sciatic nerves by means of forcible flexion of the trunk upon the thighs. The onset of the spasm one and a half minutes after the test is applied is well shown. The Leg Phenomenon of Pool. (After E. H. Pool, Annals of Surgery, 1907.)

ditional demonstration of the mechanical excitability of the motor nerves by the stretching of the sciatic and the nerves of the brachial plexus."

It would seem that the arm phenomenon had been earlier observed by the Italian clinician, Ferenczi (1904), in a boy of 14 suffering from typical tetany; but Ferenczi appears to have viewed this arm phenomenon as identical with Trousseau's sign and to have thought that it afforded evidence that Trousseau's phenomenon is of vasomotor origin, since he found that the radial pulse was scarcely palpable in the abducted arm.

In 1910, Alexander, apparently without knowledge of Pool's work, observed and reported this arm phenomenon in a case of tetany.

In the same year Schlesinger (*a*) (*b*) of Vienna reported what he desig-

nated as "a hitherto unknown symptom in tetany (leg phenomenon)." He was at that time unaware of Pool's earlier observations, but in a later paper, published in the same year, he recognized Pool's priority of observation and report. Schlesinger made an exhaustive study of the leg phenomenon (*"Beinphänomen"*), and both of his papers should be carefully read by students of tetany.

Fig. 7. The Leg Phenomenon (*Beinphänomen*). (After H. Schlesinger, Wien. klin. Wchnschr., 1910.)

To perform the test for the leg phenomenon, Schlesinger grasps the legs, with the knees strongly extended, below the calves, and flexes the thighs markedly at the hip joints. When the test is positive, spasm of the extensors of the knee and extreme supination of the foot set in after a short time, within two minutes at the latest (Fig. 7). Flexion of the toes was not observed in the first case studied. Schlesinger believed that this leg phenomenon depends upon strong flexion at the hip joint and that it will appear in both legs if the patient sit up in bed with the knees extended. Furthermore, if the standing patient flex the body on the hips, with the knees extended, the phenomenon also appears after about the same length of time has elapsed. Paresthesias regularly precede the development of the tonic contractures in the extremities examined. On the other hand, the phenomenon cannot be elicited merely by pressing upon the sciatic nerve or by pinching of the skin. Schlesinger decided that the sign cannot depend entirely upon stimulation of the sciatic nerve, since muscles that are not innervated by the ischiadicus (e.g., the extensor muscles of the knee joints) participate in the spasm. Undoubtedly the sciatic nerve is mechanically irritated on applying the test, but the motor nerves concerned must, Schlesinger thinks, be excited reflexly. The phenomenon would therefore seem to be due partly to direct, partly to reflex, stimulation of hyperexcitable nerves. The starting point of the stimulus is the stretching of the nervus ischiadicus, and this stimulation is followed

by extensive tonic spasm, owing to the peculiar and specific hyperexcitability that exists.

Schlesinger found the leg phenomenon positive 18 times in 19 cases studied He regards it, accordingly, as one of the most constant and important symptoms of tetany. The phenomenon is, furthermore, demonstrable in the different forms of tetany; for in his positive observations (including those made on 9 men, 5 women and 4 children) the majority were on cases of idiopathic tetany of workmen, two were on cases of tetania lactantium, and several were on cases of the tetania infantum of Escherich.

The leg phenomenon may sometimes be elicited very quickly, even within a few seconds. Sometimes the time of appearance of the phenomenon differs in the two lower extremities of the same patient; thus, in one instance, one extremity responded after twenty seconds, the other only after fifty seconds had elapsed. In several instances the cramp was producible in one leg only. In one case the cramp appeared first in the leg under examination and then appeared also in the leg of the opposite side not under test.

The attitude assumed by the foot is by no means always the same; sometimes there is maximal supination, so that the two soles are turned towards each other; but sometimes there is pronation with adduction. The toes are sometimes spread and extended; at other times they are spread and flexed. Occasionally plantar flexion of the foot is marked.

Though the occurrence of the leg phenomenon usually runs parallel with that of the Trousseau phenomenon in the upper extremities and sometimes with that of its analogue in the lower extremities, this parallelism cannot always be observed. In one of Schlesinger's cases the leg phenomenon appeared several days earlier than the Trousseau phenomenon.

The leg phenomenon seems to be pathognomonic for tetany. When it ceased to be elicitable in a case of tetany, Schlesinger found that, like the other symptoms, it could again be called forth after subcutaneous administration of epinephrin. Thus, within a variable period (a few minutes to an hour) after the epinephrin was administered, the leg phenomenon again became positive, the positivity continuing for several hours after the injection.

3. The Increased Electrical Excitability of the Motor Nerves in Tetany

Erb's Phenomenon

Though both Kussmaul and Benedict had noticed an increased reaction of the motor nerves to stimulation by feeble electric currents in

tetany, it was Erb of Heidelberg who first taught us that one can definitely demonstrate this galvanic hyperexcitability and make use of it as a diagnostic test. He showed also how the contraction formula alters, and he emphasized the relatively early appearance of an anodal closure tetanus and of a kathodal opening tetanus. Since he made his studies, increased electrical excitability of the motor nerves in tetany has been known as "Erb's phenomenon."

Progress in the quantitative measurement of the changes in the electrical excitability of the motor nerves in tetany was made by N. Weiss (*a*) (*b*) and especially by von Frankl-Hochwart (1886). Thus, these observers demonstrated that muscular contractions occur only on kathodal closure in normal adults in the domain of the nervus ulnaris when that nerve is stimulated with a galvanic current of 0.9 to 3.3 milliamperes, whereas in patients suffering from tetany, contractions will result from the application of a current of the strength of from 0.1 to 0.7 milliampere.

It was soon found that this hyperexcitability of the motor nerves to galvanic stimulation is one of the most constant and important symptoms of tetany. Escherich has emphasized its especial helpfulness in the diagnosis of tetany in children. In his opinion, it is the most important of all the signs for diagnosis, and this view is now held by most pediatrists.

A practical article, very valuable to clinicians who actually apply the galvanic tests, is that of Mann (1900) who collaborated with Thiemich. Mann's conclusions are as follows:—

1. For the demonstration of the increase of electrical excitability of the motor nerves in tetany, the examination of a single nerve, namely the nervus medianus, is entirely sufficient.

2. If the kathodal closure contraction (KCC) appears when the nervus medianus is stimulated with currents below 0.7 Ma. in strength, there exists an increase of excitability. If the threshold lies above this, an increase of excitability may still exist, though in that event one cannot come to a definite conclusion by testing for the kathodal closure contraction alone.

3. An increase in electrical excitability can be determined with certainty by studying the behavior of the kathodal opening contraction (KOC). This contraction appears in all cases of tetany on the application of currents below 5.0 milliamperes (usually much lower) in strength, whereas, to produce this contraction in normal persons much stronger currents are required.

4. Whereas, further, the anodal closure contraction (ACC) considerably predominates in the majority of normal persons over the anodal opening contraction (AOC), it is very common in tetany (though not entirely constant) to find the anodal opening contraction greater than, or equal to, the anodal closure contraction; or, at any rate, the strength of the currents for the anodal closure contraction and the anodal opening

contraction approach one another much more closely in tetany than under normal conditions.

5. The observation of kathodal closure tetanus (KCTe) yields only a very unreliable clew for increased excitability of the motor nerves.

6. Tests made with the faradic current also reveal in tetany, on the average, an outspokenly increased excitability of the motor nerves, but these faradic tests are not sufficiently characteristic in all cases for the recognition of increased excitability.

7. An increase of the electrical excitability of the motor nerves is demonstrable in all cases of tetany, if the above criteria be observed; and there are good grounds for the belief that cases occur in which such increased excitability is the sole symptom of the disease.

The value of testing the galvanic excitability of the motor nerves for the diagnosis of tetany in children can scarcely be overemphasized. The studies of Escherich, Ganghofner, and others early demonstrated the increase of electrical excitability of the motor nerves in tetany in sucklings, and, ever since, this increased excitability has been generally recognized as an essential mark of the syndrome.

Following upon the important studies of Mann and of Thiemich, summarized above, C. von Pirquet (*a*), in 1907, made careful studies of electrical excitability in normal children and compared the values obtained in them with those that are observable in children that suffer from tetany. Von Pirquet followed a precise technique in testing for increased galvanic excitability of the motor nerves in infants and young children. The child is laid upon its back, the large indifferent electrode upon the abdomen; the small electrode (Stintzing's normal electrode with interrupter) is placed upon the point to be stimulated.

Von Pirquet prefers to stimulate the nervus peroneus, since contractions in the nervus medianus are less satisfactorily demonstrable, on account of the finger movements that go on continuously in infants, and because tests on the facial nerve require currents strong enough to be painful. Moreover, the nervus peroneus has the advantage that it can be reached without removal of the child's shirt.

The child's left knee is seized by the left hand of the examiner, who, with his right hand, presses the stimulating electrode into the lateral part of the popliteal space. The electrode has a firmer seat there than upon the other motor point of the nervus peroneus on the lateral surface of the fibula. The mother holds the indifferent electrode upon the abdomen of the child with her left hand and with her right hand gradually alters the strength of the current of the galvanic apparatus as directed by the examiner. It is more convenient, of course, if, for the latter manipulation, one has an assistant at hand, but the procedure can be carried out with the aid of the mother alone.

At the beginning of the test the stimulating electrode is used as

kathode. The current is strengthened until it reaches about five milliamperes; there will then result, on interruption and new closure, almost always a kathodal closure contraction (KCC). The strength of the current is then diminished until contraction is no longer perceptible, when this limit value is read on the galvanometer and recorded.

The direction of the current is then changed so that the stimulating electrode becomes the anode, and an initial current with a current-strength of five milliamperes is again employed. If a contraction follow, the examiner observes whether it is a closure contraction (ACC) or an opening contraction (AOC). Each of these is then carefully followed until, on diminishing the current, it just disappears, the limit value being recorded in each instance.

The stimulating electrode is next made again the kathode; a current of five milliamperes in strength is passed through, and the examiner simply observes whether an opening contraction or a tetanus follows, for these two responses to currents of this strength are fairly equivalent signs of marked hyperexcitability.

All the findings are now recorded in the accompanying scheme (Fig. 8) which keeps kathodal closure (KCC), anodal closure (ACC), anodal opening (AOC), and kathodal opening (KOC) beside one another and is subdivided for recording current strengths of from zero to five milliamperes. Kathodal closure tetanus (KCTe) can be marked in place of kathodal opening contraction (KOC) by making use of an especial sign.

An example, illustrating the results obtained on galvanic examination of a child that had been under observation for almost a year and upon whom seventy-four tests had been made, is given in the accompanying figure. The interest in this child lay in the fact that in the course of the observation, a tetanoid state appeared, lasted for a certain period, and again completely passed off, apparently a unique observation as far as the electrical records are concerned. The child showed at first only closure contractions; then anodal opening contraction (AOC) appeared; and, later on, other symptoms of the tetanoid disease became evident, namely, the facial phenomenon and eclamptic attacks. About this time, Thiemich's phenomenon of kathodal opening contraction (KOC) first became observable. Actual tetany contractures and Trousseau's phenomenon were not present. After some weeks there was a rapid decrease in the phenomena of hyperexcitability, which died down in serial sequence the reverse of that in which they had appeared. Finally, the anodal opening contraction (AOC) also disappeared, not to reappear.

Von Pirquet was led through this observation to wonder whether or not the anodal opening contraction (AOC) has also a pathological significance, since it both preceded and followed the high grade excitability characterized by the kathodal opening contraction (KOC). Against the

pathological significance of the anodal opening contraction, however, appeared to speak the fact that it is a very common occurrence. Its average value, according to Mann, for healthy children is given as 3.6 milliamperes. Von Pirquet believes, however, on the ground of long continued examinations, that the appearance of anodal opening contractions with current strengths below five milliamperes is a sign of a mild, but nevertheless pathological, hyperexcitability. He designates it briefly "anodal hyperexcitability," because it becomes manifest at the anode, to distinguish it from "kathodal hyperexcitability," which is demonstrable at the kathode.

To kathodal hyperexcitability von Pirquet reckons, however, not simply, as Thiemich does, the appearance of kathodal opening contraction (KOC) below five milliamperes, but also the appearance of kathodal closure tetanus (KCTe) below this stimulus threshold, since his studies have shown that the two responses are practically equivalent in diagnostic significance.

Von Pirquet has happily compared the four kinds of contraction with four thermometers of different scales. Thus, the kathodal opening contraction (KOC) is a thermometer in which the quicksilver becomes visible first at 39°; with its aid we can recognize only a high "galvanic fever." For recognizing "subfebrile galvanic temperatures," if

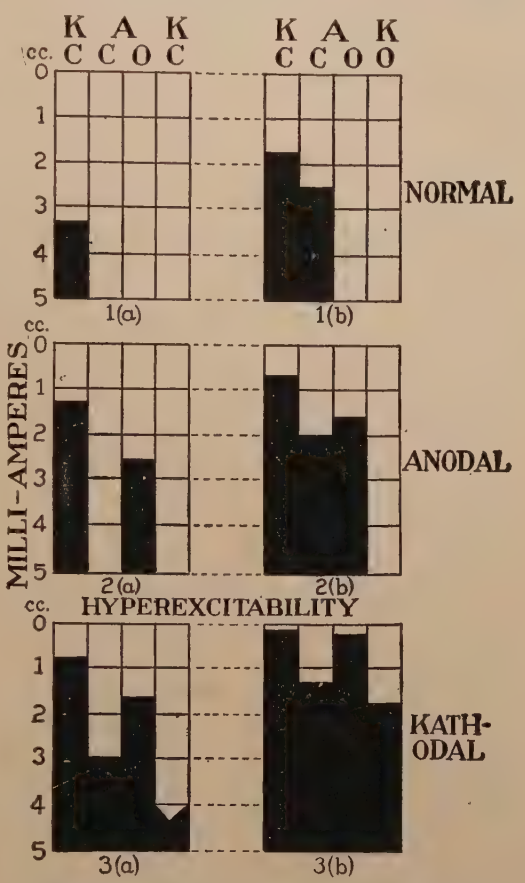


Fig. 8. Types of galvanic excitability of the motor nerves in sucklings. (After C. von Pirquet, Wien. med. Wchnschr., 1907.) Findings on testing the N. peroneus. On each excitation state, two types are chosen, between which the mean values tend to be met with. 1. *Normal excitability:* Kathodal closure (KC) only, under 5 Ma.; (*b*) KC and AC under 5 Ma. This is the normal finding in children at the end of the first year of life, whereas younger children usually approach type *a*. 2. *Anodal hyperexcitability:* (*a*) KC and AO below 5 Ma., (*b*) somewhat higher values; AC also. 3. *Kathodal hyperexcitability:* (*a*) KC, AC, AO also KCTe at 5 Ma., the latter indicated in the column of Kathodal opening by an inverted carat; (*b*) typical Thiemich reaction: All four qualities, the kathodal opening at 1.7 Ma.

the metaphor be continued, the anodal opening contraction (AOC) can be used. The kathodal closure contraction (KCC) permits of a view of even "normal galvanic temperature;" its readings are of value for indicating hyperexcitability only when contractions occur with current strengths lower than one milliampere. The anodal closure contraction (ACC) is wholly unsuitable for testing hyperexcitability, and hence one need not make use of it.

By the aid of the technique above described, very slight variations in the electrical excitability of the motor nerves can be determined. The effects of a series of influences upon the excitability of the motor nerves have already been studied with the help of this method.

Summarizing the whole matter of hyperexcitability of the motor nerves in sucklings, von Pirquet arrived at the following conclusions:—

1. Galvanic stimulation yields, in the normal suckling, only closure contractions with currents below the limit of five milliamperes.

2. The appearance of anodal opening contractions (AOC) with currents feebler than five milliamperes, when at the same time kathodal opening contraction (KOC) and kathodal closure tetanus (KCTe) are absent, is characteristic of a *mild* hyperexcitability, which one can designate by the term "anodal hyperexcitability."

3. "Anodal hyperexcitability" is a substage of "kathodal hyperexcitability," the latter being recognizable at the kathode by the appearance of closure tetanus (KCTe), or of an opening contraction (KOC) with currents below five milliamperes in strength.

Many careful studies of spasmophilia in children have been made with the aid of this exact method of studying the electrical excitability of the motor nerves. Thus, Gross's review of the work on spasmophilia, published in 1911, reported forty-two important publications for the single year. A careful study of spasmophilic children with the use of von Pirquet's methods and charts was made in the United States by Sedgwick and published in the *St. Paul Medical Journal* in 1912. The great value of electrodiagnosis in childhood tetany is made clear also in the paper of J. B. Holmes (1916). In most pediatric clinics in America today von Pirquet's method, or some modification of it, is used for the study of spasmophilia and allied conditions, and the attempt is being made to decide whether all spasmophilia in children is true tetany (or is related to it) or is to be looked upon as a condition separable from tetany.

A peculiar electrical response observed in a single instance of tetany by Bechterew should also be mentioned before the topic of galvanic hyperexcitability is dismissed. He designates it as an "excitation reaction" (*Erregungsreaktion*). The galvanic excitability of the motor nerves was markedly increased in the case he studied, but the unusual consisted in the fact that it increased even more when the electrical current was applied.

Henry M. Thomas, of Baltimore, has made a similar observation, the stimulation ending in tetanus. He believes this increased reaction on excitation to be due to the production of kathelectrotonus in the nerves and suggests that it may be called "kathelectrotonic tetanus (K. ELT. TE.). It could be demonstrated in all the nerves of Thomas's patient, who thus offered an excellent opportunity for the study of the muscular distribution of different nerves.

4. The Increased Excitability of the Peripheral Sensory Nerves in Tetany

Hoffmann's Phenomenon

Increased excitability on electrical stimulation of the peripheral sensory nerves in tetany was discovered by Hoffmann (*a*) (*b*) and is known in the literature as "Hoffmann's phenomenon." Hoffmann found that, both before and after attacks of tetany, the excitability of sensory nerves for the faradic and the galvanic currents is increased, and that the sensory formula on electric stimulation is changed very much as is the contraction formula on stimulation of the motor nerves in tetany.

Still more exact studies of this phenomenon have been made by Chvostek junior and by von Frankl-Hochwart. The subject is, however, chiefly of academic interest, since, for diagnostic purposes, the demonstration of hyperexcitability of the motor nerves is much more important.

5. The Increased Excitability of the Nerves of Special Sense in Tetany

Hyperexcitability of the nerves of special sense has also been demonstrated in tetany.

Thus, galvanic hyperexcitability of the nervus acusticus was found to exist by Chvostek junior, and his observation has been confirmed by von Frankl-Hochwart and by Schwartz.

The optic nerves and the nerves of taste have been examined for hyperexcitability also, but it is so difficult to be sure of the existence of any hyperexcitability in them that observers have been reluctant to commit themselves to any definite statement on the subject.

6. Disturbances in Autonomic Domains in Tetany

Various vasomotor, trophic, secretory and leiomyospastic phenomena have been observed by clinicians in patients presenting the tetany syn-

drome. Many of these were mentioned in the early collective reviews of Oddo (1896) and of von Frankl-Hochwart (1897) and still more of them in the compilation of Biedl (1913). Two systematic researches upon the subject are, perhaps, worthy of especial mention:—(1) that of J. Ibrahim (*a*) (1911) on tetany of the sphincters, of the smooth musculature, and of the heart in sucklings; and (2) that of Falta and Kahn (*a*) (1911), who made clinical studies on tetany with especial regard to the vegetative nervous system.

Increased Mechanical Excitability of Autonomic Nerves

Two symptoms referable to increased mechanical excitability of the vasomotor nerves observable in tetany are:—(1) *dermographismus,* outspoken in most patients in whom the syndrome occurs and (2) marked *anemia of the digits* in the distribution of the nervus ulnaris on application of a ligature to the upper arm, a symptom met with in at least one instance by Falta and Kahn.

Increased Chemical Excitability of the Autonomic Nerves

Epinephrin Hypersensitiveness.—It has been shown by Falta and Rüdinger that, in acute tetany, the effect of epinephrin on the blood pressure, the heart's action, and the constriction of the cutaneous vessels, is very marked. In normal individuals, after the injection of one milligram of epinephrin, the blood pressure and the pulse rate usually rise gradually, whereas in acute tetany there is a very quick rise of both blood pressure and pulse rate, the acme being reached within two minutes, and, at the same time, marked pallor of the face and of the skin of the whole body is observable. The accelerated heart's action is sometimes accompanied by premature beats or by subjective feelings of palpitation.

In almost all cases of tetany, an acute exacerbation of the common symptoms of the syndrome follow the injection of epinephrin. Thus, Falta and Kahn observed in their cases a return of the paresthesias, an aggravation of the Chvostek and of the Trousseau phenomena, the recurrence of spasms in the muscles of the extremities, of the trunk, of the glottis, and of the respiratory apparatus, including the diaphragm. As the tetany dies down, the effects of epinephrin injections become less pronounced. In single cases of acute tetany the augmenting effect of epinephrin upon the symptoms is less marked, or may not be observable at all.

Elliot (1905) pointed out that the vasodilators respond earlier to minimal sympathicotropic stimuli than do the vasoconstrictors; hence, vasodilatation is an especially delicate reagent for testing the excitability of the vasomotor nerves. Falta and Kahn's experiments indicate, they

believe, that, in tetany, the site of the hyperexcitability for sympathicotropic stimuli is the myoneural junction.

Pilocarpin Hypersensitiveness.—As was shown by Eppinger and Hess, pilocarpin is a substance that stimulates especially the craniosacral portion of the autonomic nervous system. Symptoms due to such stimulation include hyperhidrosis, salivation, lacrimation, goose skin, vasodilatation in the skin, and feelings of heat and of congestion in the head. All these signs that follow the injection of pilocarpin are much more marked in patients suffering from acute tetany than they are in normal persons.

Injection of pilocarpin also increases the ordinary signs of tetany and may call forth the tetany spasms in different muscle domains. Thus, spasm of the glottis and of the muscles of deglutition have been observed to follow pilocarpin injection. Hypersecretion of the stomach juice, and hyperperistalsis of the intestine with diarrhea, may also follow pilocarpin injection.

Certain Symptoms Indicating Hyperexcitability of the Vegetative Nervous System

Observations of spontaneously occurring signs of hyperexcitability in craniosacral and sympathetic vegetative domains have been assembled in the articles of Ibrahim and of Falta and Kahn. These interesting signs may be briefly referred to.

Spasm of the Intrinsic Muscles of the Eye.—In this domain there have been noted: (1) spasm of the M. ciliaris and (2) spasm of M. dilator iridis, usually of one side only, with resulting anisocoria.

Lacrimation, Salivation, and Hyperhidrosis.—In a man of thirty-one Falta and Kahn observed outspoken lacrimation in the tetany attacks, with slight hyperemia of the conjunctivæ; and these symptoms were associated with increased flow of saliva. Hyperhidrosis was also observed by them in three cases, but as one of the patients was tuberculous and the others had slight signs of hyperthyroidism, it is not certain that the increased tendency to sweating was due to the tetany.

Disturbances of Respiration.—Tachypnea in tetany has been described by Ibrahim, and by Finkelstein (*a*). Dyspnea is also frequently observable.

Disturbances of the Action of the Heart.—Ibrahim observed three cases of sudden death in tetany in sucklings without spasm of the glottis and without any signs of asphyxiation at autopsy. In two of the cases, the heart was dilated. In one of them, the right heart was relaxed, whereas the left ventricle was markedly contracted and firm. Ibrahim assumed that he had to deal with tetany of the heart, perhaps called forth by hyperexcitation of the vagus or of the sympathetic.

In a case of tetany following strumectomy, recently observed with Dr. Sydney Miller, of Baltimore, and already referred to above, the sudden

death that occurred about two weeks after the operation may possibly have been due to tetany of the heart, but since the patient had a moderate grade of arteriosclerosis with hypertension and complained of pain in the left shoulder, it is possible that we had to deal simply with a case of angina pectoris independent of the tetany. No autopsy could be obtained, which was unfortunate, for it would have been interesting to have learned the condition of the aorta and of the coronary arteries.

Falta and Kahn have called attention to the increased action of the heart manifested by loud tones at the apex, and by slight tachycardia on mental excitement and on exertion in the acute stage of tetany. They think it certainly established that, in the acute stage of tetany, the heart muscle, at least in very many cases, contracts with increased force, but they are unable to decide whether this state of excitation is localized in the autonomic heart ganglia or in the extracardiac heart-regulating nerves. They think it very probable that, owing to hyperexcitability of the nerves regulating the heart, its action is sometimes markedly influenced in tetany, and they adduce Ibrahim's observations of three fatal cases in which he supposed that death was due to tetany of the heart in favor of their view.

Vasomotor Disturbances.—Falta and Rüdinger (1909) called attention to their observations showing that all tetany patients, in the acute stage, exhibit outspoken vasomotor disturbances. Among these may be mention:—(1) Outspoken dermographismus; (2) abnormally marked variations of tonus on psychic stimulation, and, especially, on emotional stimulation; (3) facial pallor, even when the blood shows an abnormally high red cell count and when there is no diminution in hemoglobin (in one case with facial pallor the red blood count was 7,808,000); (4) edematous swellings due to angiospasm; (5) dead fingers; (6) complaints of congestion in the head; and (7) "pudgy" look to the face, but without the lividity in the middle of the cheeks seen in myxedema.

Functional Disturbances in the Gastrointestinal Tract.—On making careful functional tests in the domain of the digestive apparatus most patients with tetany will be found to exhibit milder or more severe functional disturbances of the stomach, of the intestines, or of both. These include gastric hyperchlorhydria, pylorospasm, and other forms of gastrospasm, intestinal hyperperistalsis, and diarrhea.

Changes in the Blood Count.—Friedrich Müller, Fleiner (*a*) (*b*), Falta, and others have reported increased *red cell counts* in acute tetany, and especially during the tetany attacks. The polyglobulia that follows the injection of epinephrin seems to be greater in tetany than in normal persons. It has been suggested that these polyglobulias may be due to vasospasm with passage of the fluid plasma into the tissues. In this connection, the experimental work of Paul Lamson on the outflow of red corpuscles from the liver after the injection of epinephrin should be borne in mind.

The total *white cell count* does not seem to be markedly altered in tetany, but the differential formula is often changed in the direction of a relative lymphocytosis with a relative and an absolute diminution of the polymorphonuclear neutrophile cells. Whether this is due to a complicating status thymicolymphaticus, believed by Escherich to be common in childhood tetany, is not yet certain. In accord with Escherich's view might be cited the experimental work of Uhlenhuth (*vide infra*).

Sudden transformations of the differential formula of the white cells are looked upon by Falta and Kahn as an expression of isolated states of excitation in the domain of the vegetative nervous system, with predominance sometimes of sympathetic influences, sometimes of craniosacral autonomic influences.

Disturbances of Heat Regulation.—Disturbances of temperature regulation have been described in tetany by various observers since 1830. In Dance's article elevation of temperature was mentioned; and, later on, Hoffmann, von Jaksch, and von Frankl-Hochwart all called attention to the subfebrile temperatures that may be met with in tetany. I refer of course to the disturbances of heat regulation that are independent of infections. The fever, as described by the earlier observers, was usually remittent or, more rarely, intermittent in character. Slight fever in childhood tetany has been described by Loos and by Cassel, in the absence of gastrointestinal affections and of infectious diseases.

In experimental tetany in dogs elevations of temperature are common during the attacks. According to Falta and Kahn, certain patients, in the acute stage of tetany, exhibit elevations of temperature after injections of substances (antithyroidin, pituitrin) that in healthy persons cause no fever, and they suggest that the disturbances of heat regulation in tetany are probably an expression of states of excitation of the vegetative, especially of the sympathetic, nerves.

Symptoms Pointing to Depression, Rather than to Excitation, of the Visceral Nervous System

Interesting experiments made by A. J. Carlson (*a*) of Chicago (1912) indicate that there may be depression, rather than increased excitability, of the visceral nervous system in experimental tetany. Thus, he found that no spasms, contractures, or other evidence of hyperexcitability, and no tetany of the neuromuscular mechanisms of the digestive tract occur in the parathyroid tetany of cats and dogs. The deviation from the normal is, he asserts, in the direction of depression or paralysis, rather than in that of overstimulation or hyperkinesis. He found, too, that the gastric and pancreatic digestion, though usually retarded in tetany, may be normal, but slowing of the digestive processes is the rule and there may even be total failure of digestion in these animals in tetany. In

exceptional instances he observed acceleration of gastric digestion in tetany cats.

The retarded digestion in experimental tetany is not due, Carlson asserts, to the absence of appetite secretion, nor to splanchnic inhibition, but is rather the effect either of the direct action of chemical substances in the blood upon the digestive glands, or of an alteration of activity dependent upon the absence of the parathyroid secretion.

Carlson maintains further that the deviations from normal activity in parathyroid tetany in cats and dogs, as far as the other sympathetic and autonomic mechanisms are concerned (visceral sympathetic, pilomotors, sweat nerves, uterus, bladder, sphincters), is in the direction of depression rather than of excitation. It is obvious, therefore, that more studies should be undertaken before these discordant results of observations in human tetany and in experimental tetany can be satisfactorily explained.

Trophic Disturbances in Chronic Tetany

In chronic tetany interesting dystrophies, especially of structures of ectodermal origin, are common. Thus, the nails, the hairs, the teeth and the crystalline lens may all exhibit signs of trophic disturbance.

Nails.—Herard (1843) described a patient, 36 years old, with severe tetany, who shed his finger nails; and Meinert observed falling out of the nails in tetania gravidarum in a washerwoman. Ewald described falling of the nails in a case of tetany associated with dilatation of the stomach. Hoffmann saw a single finger nail fall out in a case of childhood tetany. Similar observations have been made in other forms of tetany. Brittle nails, grooved nails, and necroses of the roots of the nails have all been mentioned as occurring in cases of tetany.

Hairs.—Falling out of the hair has been several times met with in chronic tetany. Fortunately, the hair sometimes returns after the attacks of tetany have passed off. A Dutch observer, Bolten (*b*) (1917), has recently described a case of latent tetany in which the hair of the head, the eyebrows, and the body hair fell out. He looked upon the loss of hair as a trophoneurosis due to the latent tetany. General defluvium of the hairs may, of course, occur in conditions other than tetany.

Teeth.—Most remarkable alterations in dentition in early life, as well as peculiar enamel defects in the teeth in later life, have been observed in tetany.

Thus, in rats, the experimental tetany produced by Erdheim (*e*) ran a very chronic course, the animals surviving operation for from two to five months, or even longer. These animals were found to show constant changes in their teeth, namely, circumscribed enamel defects, sometimes so marked that the teeth easily became fractured. The changes in the teeth in these rats interfered so much with the mastication of food that

they played a considerable part in the production of the marked emaciation and cachexia that characterized these animals. Erdheim made histological studies of the teeth in such experimental rats, and found that the trophic disturbances in the teeth appeared quickly after the injury to the parathyroid glands. He was able to demonstrate (1) a faulty calcification of the dentin and (2) hypoplasia of the enamel.

A comprehensive study of the finer histological changes in the teeth in experimental tetany in rats has been made by Toyofuku (1911), working under Erdheim's direction. He has described in detail the faulty calcification of the dentin, and the peculiar changes in the enamel that are observable after removal of the parthyroid glands of these animals.

Erdheim himself (1911) succeeded, by performing autotransplantation of parathyroid glands immediately after extirpation, in producing a temporary status parathyroprivus, which was again abolished after the graft had taken. A most interesting result of this experiment was observed. A narrow strip of dentin, poor in calcium, corresponding to the period of status parathyroprivus, appeared and persisted. Erdheim, by this and similar experiments, sought to prove that teeth undergoing development at a time when a status parathyroprivus occurs show permanent enamel defects.

Stimulated by these interesting researches of Erdheim on experimental tetany in rats, L. Fleischmann (1907-9) made exhaustive studies of the trophic changes in the teeth of children in rickets and in tetany. The findings in rickets, though very important, do not concern us here, but in cases of infantile tetany, along with the dentin changes due to rickets, he found characteristic changes in the enamel due to the tetany. These changes consist in defects in the enamel covering of teeth—true hypoplasias of the enamel. They take the form of little pit-like depressions, arranged often in rows extending horizontally across the tooth. Sometimes a single row of such pit-like enamel defects is seen; sometimes two or three parallel rows superimposed one above another running around the whole circumference of the tooth. Fleischmann further demonstrated that persons who have had tetany in the first or second year of life, that is at a time when certain of the teeth develop (most often the first molars, the medial upper incisors, the canines, and the inferior incisor teeth), carry throughout life typical enamel defects, whereas, when the tetany occurs between the third and fifth years of life, the enamel defects are found on the second bicuspids, the second molars, and the wisdom teeth. Fleischmann emphasizes the fact that it is not single teeth that show these hypoplasias of the enamel; they are in evidence on all the teeth that happen to belong to the developmental period of the time when the tetany occurred. He asserts that these enamel defects have nothing to do with rickets, as was formerly supposed, but are wholly due to the

tetany, or, rather, to the disturbance of parathyroid function and of the calcium metabolism underlying it.

A good illustration of the enamel defects in the teeth of an adult male who had had tetany in childhood will be found in Fig. 9, taken from Phleps's article on tetany in Lewandowsky's *Handbuch*. I had myself observed such enamel defects in adult human beings in more than one instance; before I learned of the work of Erdheim and of Fleischmann I had no idea of their cause. The J. P. Munroe case of chronic tetany reported at Charlotte, N. C., showed this enamel dystrophy in high degree.

It is well to be always on the lookout for these enamel defects when examining patients, for, if found, they prove that the patient has had tetany in early life and not infrequently they give the clew, too, to the presence of a chronic tetany still existent. When parallel rows of enamel defects are visible in an adult, as in the figure, the terrace-like or staircase-like appearance of the teeth permits one to assume the existence of a recurring tetany during the developmental period. Patients presenting such enamel defects should be questioned regarding the occurrence of laryngospasm and other muscle spasms in earlier life. Especially, if the parents of such a patient be still living, it will sometimes be possible to secure from them a history that points to tetany in the early childhood of their offspring.

Crystalline Lens.—The crystalline lens is made up, as is well known, of epithelial cells, so arranged that some are centrally placed (nucleus of the lens), others peripherally placed (cortex of the lens).

Clinicians have long known that persons suffering from attacks of tetany are especially prone to the development of cataract. Thus, Landsberg (1888), von Eiselsberg, Hoffmann (1897), Westphal (1901), and Wangenmann (1902) reported cataract developing in human beings after tetania strumipriva. And after attacks of idiopathic tetany, the development of cataract was observed by Bernhardt (1891), Wettendorfer (1897), Peters (1898), Freund (1899), Uhthoff (1901), Saska (1904), and others. After tetania gravidarum, too, cataract has been observed by a number of clinicians.

Even in the tetany of children cataract may appear, Peters (1901) having observed distinct turbidity of the deeper cortical layers of the lens in both eyes in a child three years old that had suffered from several severe attacks of tetany. He has reported, too, a similar opacity in the lens of a seven-year-old girl, and, still more interesting, he has described tetany and beginning cataract in the children of a mother who had recovered from tetania gravidarum. One of these children was eight years old, the other four. An older sister of these two children had a central cataract, though, as far as was known, she had never suffered from tetany. Peters has emphasized, therefore, the importance of careful examination of the eyes in children that have had tetany.

Pineles (*b*) (1905), in a collective review, brought together from the literature all the cases of cataract reported as occurring in the different forms of tetany. The cataract following tetany may be either perinuclear or central. Peters, in the course of a single year, observed no less than thirty tetany cataracts, and Zirn (1905) reported having observed six tetany cataracts in the course of four months work. Five of the patients exhibiting tetany cataract also suffered from falling out of the hairs and nails; four of the cataract patients suffered from pregnancy tetany. It seems probable that the cataract in tetany is due to toxic changes in the ciliary epithelium rather than, as was earlier thought, to spasm of the ciliary muscle.

Conjunctivitis.—It was pointed out by De Quervain that parathyroidectomized dogs very often suffer from marked conjunctivitis. Falta and Kahn found conjunctivitis almost constantly in dogs and cats that had been deprived of their parathyroids. The same authors have described a human case of tetany, in which conjunctivitis occurred; the conjunctivitis regularly underwent exacerbation at times when the tetany was worse.

7. Psychoses in Tetany

Attacks of tetany are, as a rule, accompanied neither by loss of consciousness nor by marked disturbances of consciousness. In some instances, however, clouding of consciousness has been met with in tetany (Müller) and combinations of tetany with outspoken psychoses have several times been reported (Arndt and others).

In 1889 von Frankl-Hochwart published a careful description of certain cases in which hallucinatory confusion accompanied tetany, and Kräpelin made several observations on cases in which psychoses occurred in combination with typical signs of tetany. In such cases the tetany seems to have appeared at first in only moderate severity. With exacerbation of the spasms, the hallucinatory confusion set in, to disappear later as the spasms passed off. Even in the intervals between attacks the patients sometimes complained of disturbances of mood or of excitement.

In chronic tetany mental dullness and enfeeblement of memory are not uncommon, especially in the form of chronic tetany that sometimes follows strumectomy; in these cases, however, hypothyroidism may play a part in the origin of the psychosis.

An important paper by A. M. Barrett of the State Psychopathic Hospital at Ann Arbor, entitled "Psychosis Associated with Tetany," was published in the *American Journal of Insanity* in 1920. On a careful review of the literature, Barrett found no less than sixty-seven references bearing upon the subject. He concludes that there is no specific tetany psychosis, but that the neuromuscular disturbances and the psychosis are

both the result of a toxic process affecting the central nervous system. In two cases that came under his own observation, lesions (cysts) were found in the hypophysis cerebri, and he thinks the psychoses in these two instances may have been related to the hypophyseal disease.

8. Tetany and Epilepsy

A collective review of the whole literature on the relationships of tetany and epilepsy was published, in 1911, by Emil Redlich of Vienna, in the *Monatsschrift für Psychiatrie und Neurologie*. Redlich had, himself, observed eleven patients in whom tetany and epilepsy (or at least epileptiform attacks) had occurred together. This experience led him to study the cases reported since 1891, when this combination had first been observed. He found altogether, in addition to his own case, forty-six definite instances reported in the literature, and also twenty-six cases that had been less well described, that is some seventy-two cases in all.

Redlich divided the cases of combined tetany and epilepsy into groups:—(1) patients who have had typical epilepsy for years, or those who earlier have had at least one attack of epilepsy, and who, later, have exhibited temporary, often recurring, phenomena of tetany; and (2) cases of tetany in which, during the course of the tetany, or simultaneous with its onset, epileptic attacks have set in.

In the first group of cases, the epilepsy and the tetany need not necessarily stand in etiological relationship, whereas, in the second group, an etiological-pathogenetic connection is more probable. Of the second group, twenty-one were cases of tetania parathyropriva following strumectomy, seventeen were cases of juvenile idiopathic tetany (epidemic-endemic form), five were cases of maternity tetany, and the others were cases of epilepsy in infantile tetany and in gastric tetany.

It is interesting that fifteen out of the seventeen patients with epilepsy in tetania parathyropriva after strumectomy were women; only two were men; whereas, among sixteen examples of epilepsy in epidemic-endemic tetany, eleven were in men and five were in women. As is well known, men are much more often affected by idiopathic tetany than are women.

Certain peculiarities of the tetany and of the epileptic attacks were noticeable in the idiopathic tetany group. Thus, in one case, the tetany attacks remained for years limited to the right side; in another, the epileptic attacks began by the assumption of the tetany position in the left upper extremity; in still another case, the epileptic attacks were preceded for hours by tetany spasms. In a case observed by Luger epileptic attacks appeared when testing for the leg phenomenon. After the epileptic attacks the Erb phenomenon and the Trousseau phenomenon

appeared to become, as a rule, more marked. Several of the cases of tetany with epilepsy exhibited signs (choked discs, paralyses, etc.) pointing to organic brain disorder. Three of the cases of epilepsy combined with maternity tetany were observed in Vienna, a region in which tetany is endemic.

The question of the pathogenetic relationships of childhood tetany (and of spasmophilia) to epilepsy has always interested clinicians and has been discussed by both pediatrists and neurologists. In six cases of epilepsy after childhood tetany, described by Redlich from his own experience and from the literature, the age of the persons at the time of the observation was three, nine, ten, fourteen, twenty-three, and twenty-four years respectively; but the epilepsy had existed in all of them from childhood on; in part of them it dated from the suckling period. There was no history of epilepsy in the family of any one of these six patients, though in one case the child had suffered from congenital lues and in several of the cases there were evidences of constitutional inferiority of one sort or another (idiocy, hydrocephalus, marked obesity, infantile myxedema, mongolism). Enamel defects in the teeth were observable among these children. Chvostek's phenomenon was present in them, too, but Redlich asserts that it is often present (independent of tetany?) in epilepsy and in other nervous diseases (including dementia precox, hysteria, neurasthenia, and Graves' disease). Chvostek's phenomenon is known to be very common in children and to grow less frequent in later life. Though Redlich admits that mild tetany may be much more common in childhood than is generally thought, he is unwilling to go so far as to assume that the presence of a Chvostek sign necessarily means the existence of tetany.

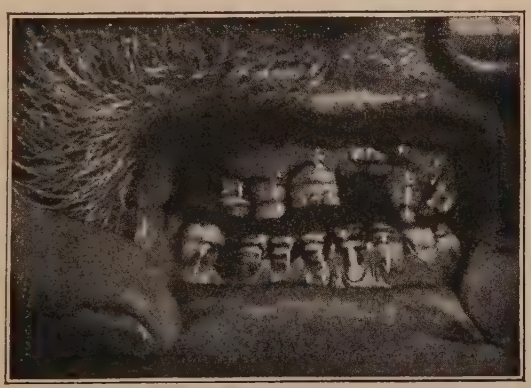


Fig. 9. Trophic disturbances (dystrophy) of the teeth in a case of chronic recurrent tetany with no traces of rachitic bone changes. Note the parallel grooves due to enamel defects. (After E. Phleps, in Lewandowsky's Handb. d. Neurol., published by J. Springer, Berlin.)

Under spasmophilia, or the spasmophile diathesis of Finkelstein, Thiemich included tetany, laryngospasm (which in most cases belongs to tetany), and, finally, eclampsia infantum. He, however, separated the latter from epilepsy, despite its resemblance to epileptic attacks. He believed that eclampsia infantum can be separated from true epilepsy through the circumstance that, in the former, spasmophile phenomena

(laryngospasm, manifest tetany, Chvostek sign) are present, or, if these be absent, the decisive electrical hyperexcitability of the motor nerves, at least, is demonstrable. Further characteristics of the spasmophilia that he mentions as serving to separate eclampsia from true epilepsy are the seasonal appearance of the attacks, the influence of diet, and the accompanying rachitis. Spasmophilia is an exquisitely hereditary and familial disease, which, he believes, stands in relation also to general neuropathic inferiority.

Birk accepted Thiemich's views and enlarged upon them. One of his strongest arguments for separating eclampsia infantum from epilepsy is the ultimate fate of spasmophile children. He reported, in 1907, fifty-three cases in which there had been spasmophilia in early childhood. In none of these had epilepsy developed. They had recurrences of their spasmophile phenomena, it is true, but their attacks were never, he asserted, of epileptic nature; they were characterized by the appearance of Chvostek's sign, and by demonstrable electrical hyperexcitability of the motor nerves. Though epilepsy does not develop from spasmophilia, Birk believed that there is a tendency in these children to an unfavorable prognosis in another direction. Thus, on analyzing his cases, he found that only one third were normal in later life; two thirds of them did badly in school, were intellectually and emotionally inferior, or exhibited pavor nocturnus, headache, and other neuropathic phenomena. That there is no history of epilepsy in spasmophile families is a strong argument, Birk thought, against the identity of spasmophilia and epilepsy.

Another view of the relationships of eclampsia infantum, spasmophilia, and epilepsy is that represented by Potpeschnigg. This author asserted that most eclampsias have nothing to do with Thiemich's spasmophilia, but their spasms result rather from carbon dioxid poisoning, due to the laryngospasm. Of the eclamptic children he had studied, a number had already become epileptic, and he believed that more would become epileptic later. It is obviously desirable that neurologists and pediatrists should, together, from now on, study these cases of convulsions in children in order that greater unity of opinion may gradually emerge.

When epileptic attacks follow tetania parathyropriva after strumectomy, there is, Redlich believes, no organic brain lesion; nor does, in these patients, hereditary or acquired disposition to epilepsy play any special rôle. In these cases it is the tetany itself that must be the cause of the epileptic attacks. The matter is not quite so clear, Redlich thinks, for the epilepsy that may be associated with other forms of tetany, and the results of further studies must be awaited before the relationships in these groups of cases are satisfactorily explained. That the tetany itself may be responsible in some instances seems probable, but it is also likely that, in others, the association is merely accidental.

9. Tetany and Myotonia

Myotonic symptoms have often been met with in patients exhibiting the tetany syndrome; but the tetany in such patients has often been atypical and there has been much discussion as to the exact nature of the relationship existing between the tetany and the myotonia.

Von Frankl-Hochwart observed myotonic phenomena in the tetany of a patient who, later, was found to have syringomyelia. Myotonic symptoms are by no means uncommon in syringomyelia, and Schlesinger has even described a "myotonia syringomyelica." Important papers on the subject have been published by Lundborg (*b*), Bartels, Erb, and others. Cases have been reported in England by Risien Russell and in the United States by Jacoby (1898). An extensive collective review of the whole subject of the relations of tetany and myotonia, with reports of cases personally observed, has been made by von Orzechowski (1909).

Of the myotonic symptoms most often observed in certain cases of tetany, in addition to subjective complaints of stiffness when starting to walk, may be mentioned (1) intention spasm on opening and closing the mouth (masseter muscles) and on opening the fists, (2) general increase of muscular excitability, (3) sluggish contraction of the muscles, (4) spasm on opening and closing of the eyelids, (5) stiffening of the hands on immersion in cold water, (6) familial character of the malady, and (7) onset at puberty.

On analyzing critically all of the cases that had been reported, von Orzechowski arrived at a number of interesting conclusions, among them the decision that the myotonic syndrome met with in certain cases of tetany is, in the mechanism of its origin, entirely independent of the principal symptom of tetany, which is the general increase in the excitability of the motor nerves. In cases of tetania myotonica it is exceptional to find a complete syndrome of tetany along with a complete myotonic syndrome.

The cases in the literature of tetany combined with myotonia can, according to von Orzechowski, be divided into three groups:

A. Complete tetany syndrome with single myotonic symptoms.

B. *Formes frustes* of tetany with *formes frustes* of the myotonic syndrome.

C. Well developed myotonia with single tetany signs.

The endocrine relationships of tetania myotonica are difficult to unravel. The fact that, in tetania myotonica, either the tetany syndrome or the myotonic syndrome is usually incomplete depends apparently upon an antagonism of the symptoms of the two categories, each set tending to suppress the other. Von Orzechowski suggests that in these combined cases of tetany and myotonia we have to deal with a dysparathyrosis

rather than with a simple hypoparathyrosis, as in tetany. The possibility that some gland of internal secretion, in addition to the parathyroids, may be involved has also to be considered. He thinks it very probable, too, that many cases of acquired myotonia have something, as far as pathogenesis is concerned, in common with tetania myotonica.

The possibility that a disturbance of internal secretions may exist in many cases of pure acquired myotonia, and the facts of the familial appearance and of abnormal constitutional makeup in many cases of tetania myotonica, speak in favor of a similar endocrine pathogenesis for true Thomsen's disease (myotonia congenita), especially since single symptoms of tetany are not rare in the latter disease. The usual absence of symptoms of tetany in Thomsen's disease may be explained, von Orzechowski believes, by the tendency to reciprocal suppression, the symptoms of tetany in this instance being wholly suppressed by the myotonia. In the present state of our knowledge, it is fair to assume that the tetany symptoms in tetania myotonica are due to hypoparathyrosis, but we must admit, I think, that we are as yet completely in the dark as far as any explanation of the myotonic phenomena themselves is concerned.

10. The Reflexes in Tetany

On account of the now well known hyperexcitability of the motor and sensory nerves in tetany, one might expect to find the deep or tendon reflexes always exaggerated in this syndrome. As a matter of fact, this is not the case. It is true that they are increased in some patients, but they are normal in others; and, in perhaps the majority of instances, they are decreased, especially at the time of spontaneous paroxysms and in the periods immediately following them.

Anomalies of the superficial reflexes (abdominal, plantar) do not seem to have been observed in tetany.

11. Sensory Tetany

Paresthesias, especially acroparesthesias, are very common in tetany; they constitute a part of the classical syndrome. These paresthesias often appear as prodromata to the outbreak of spontaneous attacks of tetany spasm. Grant and Goldman, in the tetany of forced respiration describe the constant occurrence of paresthesias before the onset of the tetany spasms.

In some instances paresthesias may appear as "equivalents" of the motor tetany attack.

F. Parkes Weber (1911) has suggested that the numbness and tingling

in the hands and feet (acroparesthesia) and the motor symptoms of tetany may be regarded as analogues of the paresthesias and the vasomotor phenomena known as Raynaud's disease. Raynaud's disease might, he thinks, be designated "vasomotor tetany," just as acroparesthesia might be termed "sensory tetany." Weber even hints that they may all have a similar etiology.

12. The Skin in Tetany

In addition to the hyperhidrosis, the dermographismus, and the erythemas observed in tetany (already described under disturbances of the vegetative nervous system), one meets, in the literature of tetany, reports of pigmentations and of outbreaks of urticaria and of herpes. These complications are, however, relatively rare, and it is by no means certain that they are not merely accidental associations, not definitely related to the main process.

13. The Muscles, Bones and Joints in Tetany

Joints.—Joint swellings have often been mentioned in descriptions of tetany. It will be remembered that one of the earliest observers of tetany, Steinheim, regarded the disease as a peculiar form of rheumatism. Some of the joint symptoms described were doubtless complicating arthritides; others seem to have been more of the character of intermittent hydrops.

Muscles.—The tonic muscle spasms characteristic of manifest tetany have already been described (*vide supra*) and mention has also been made of the fibrillary twitchings and the clonic contractions that are occasionally seen. Paresis of muscles has frequently been observed in tetany and is an important though a frequently overlooked part of the tetany syndrome. True muscular atrophy, as well as true muscular dystrophy, has sometimes, though rarely, been observed in association with tetany.

Bones.—The bones have been but little studied in human tetany, though Schüller has described a form of osteoporosis observable in x-ray plates. Attention has often been directed, too, to the frequent association, in childhood, of tetany with rickets.

The bone changes in experimental tetany have been carefully described by Erdheim. After removal of the parathyroid glands in young rats, he found that the newly forming bone tissue in the developing skeleton failed to become calcified, or, if calcification occurred, it was delayed and incomplete. The lime-poor bone tissue resembled that observable in rickets and in osteomalacia.

Interesting studies of the skeleton in experimental chronic tetany,

produced in young rats by parathyroidectomy followed by transplantation of parathyroid tissue into the spleen, have been made by Iselin. The animals were retarded in their growth and röntgenological examinations of their skeletons revealed a diminution in the size of their bones, though their normal forms were preserved. The histological changes in these bones resembled more closely those of rickets than those of athyreosis.

Fractures of bones heal less well in hypoparathyroidism than in normal animals (Canal, Morel), owing to delayed ossification of the callus, a defect that can apparently be overcome by the administration of parathyroid gland substance.

14. The Endocrine Glands in Tetany

Parathyroid Glands

That the symptoms of tetany are identical with those that follow removal of all, or of a part, of the parathyroid glands, has been definitely proven both for animals and man. Every one now agrees that tetania strumipriva is, in reality, a tetania parathyropriva, and the majority of clinicians and experimental physiologists believe that, in several, if not in all, the other forms of tetany, we have also to deal with parathyroid insufficiency. The relation of the parathyroid glands to tetany is so fully discussed in other sections of this article (see Historical Notes and Etiology and Pathogenesis) that further comment here is unnecessary.

Thyroid Gland

Some investigators hold that the thyroid and the parathyroids are organs that can reciprocally, in case of need, act, to a certain extent, vicariously one for the other; others maintain that no such reciprocal vicariousness of function is possible, and that the thyroid and the parathyroids are functionally antagonistic organs. The evidence thus far available scarcely suffices for the complete substantiation of either view, and more work must be done before the matter can be considered to be settled.

Those who support the doctrine of reciprocal antagonism can adduce many observations that they think favor it. Thus, the tetany that follows simultaneous extirpation of the thyroid gland and the parathyroid glands seems to be of a milder type than that which follows parathyroidectomy alone. It has been suggested that this relative mildness is due to a lack of the reënforcement by the thyroid of the parathyroid insufficiency produced by extirpation of the parathyroid glands; if the thyroid were not removed the parathyroid defect would be more strongly in evidence.

It has long been known that, when the thyroid gland is extirpated, metabolism is slowed up and the excitability of the whole nervous system is diminished; and this change in the general and especially in the nerve metabolism may help to explain why the hyperexcitability of the nerves that follows parathyroidectomy alone is lessened by simultaneous removal of the thyroid. Halsted (*a*) (1907) reported some experiments on dogs, made by him in 1888, that might be valued in support of this view. In these experiments, the two superior parathyroids of the dogs were probably deprived of their circulation. After the operation, hypertrophy of both thyroid lobes developed, and the animals exhibited the signs of chronic tetany. Halsted suggests that possibly the chronic tetany appeared because the hypertrophied thyroids were imperfectly equilibrated by the two parathyroids, and that, if thyroid hypertrophy had not resulted from the experiment, the two inferior parathyroids would have been more than ample for the prevention of tetany.

In addition to the experiments of Halsted, there are in the literature reports by a number of other investigators of experiments that indicate that parathyroidectomy is regularly followed by hypertrophy of the thyroid gland (Edmunds, Lusena, Vassale and Generali, Halpenny and Thompson).

When, on the other hand, the thyroid gland is removed, hypertrophy of the parathyroid glands develops. This hypertrophy occurs in the external parathyroid glands of the rabbit after extirpation of the thyroid gland and the internal parathyroids (Gley, Halpenny and Thompson, Biedl). Hypertrophy occurs in the internal parathyroids of the rabbit after extirpation of the external parathyroids and of the accessory parathyroids in the thymus (Haberfeld and Schilder). And in young dogs, the intact parathyroids left behind at thyroidectomy were found a year later by Biedl to be twice as large as those of control animals of the same litter. Rüdinger assumes that this hypertrophy of the parathyroids after thyroidectomy is due to the loss of function of an antagonistic organ (the thyroid). Normally, he maintains, the function of the one gland is controlled by that of the other, whereas, when this normal control is removed, the organ left behind becomes functionally overactive and later shows anatomical hypertrophy.

In support of the theory that the thyroid and the parathyroids are reciprocally antagonistic organs, Rüdinger has adduced certain other observations, namely (1) the clinical reports according to which myxedema patients were made worse and a patient suffering from Graves' disease was benefited by the administration of parathyroid gland substance (Moussu and Charrin), (2) the favorable effects of the serum of Möbius (from thyroidectomized animals) and of rodagen (made from the milk of thyroidectomized goats) in Graves' disease (attributed by Walbaum and by Rüdinger to the accumulated parathyroid secretion that resulted from

the removal of the antagonistic thyroid), and (3) the observations of Eppinger, Falta, and Rüdinger on the difference in behavior of thyroidectomized and thyroparathyroidectomized dogs on the administration of epinephrin, a difference that they thought pointed to an antagonism between the thyroid and the parathyroid glands.

Those who advance the view that the thyroid and the parathyroids are not antagonistic organs, but, on the contrary, are organs that are capable of vicariously functioning one for the other in case of need, interpret the observations referred to above in favor of their own theory and bring forward still other observations and experiments in its support. Thus, Biedl, analyzing Rüdinger's arguments, points out that (1) a correlative hypertrophy of antagonistic organs has not hitherto been demonstrated and, moreover, is difficult to understand; and (2) the therapeutic effects of Möbius' serum in Graves' disease, which, independent of all therapy, often shows extraordinary variations in the intensity of its symptoms, are of but little value in the support of any hypothesis. Biedl himself thinks that the phenomena of hypertrophy of the parathyroid glands after thyroidectomy point rather to a compensatory process, and is inclined to share the hypothesis of Vincent and Thompson, who look upon the thyroid, the parathyroids, and the pars intermedia of the hypophysis cerebri as organs belonging to one functionally connected apparatus, the parts of which possess in common a capacity for vicariousness of function.

Arguments from the histological side have been submitted in favor of the view that these organs are not antagonistic to one another. Gley had early surmised, from his anatomical and histological studies, that the parathyroids could hypertrophy and take over in part the functions of the thyroid gland after thyroidectomy. Notwithstanding the fact that embryological, experimental physiological, and clinical studies have demonstrated the morphological and functional independence of the parathyroid glands and the thyroid gland, Vincent and his pupils have recently reemphasized the histological resemblance of the structures in the two organs, not only under normal conditions, but also when pathological changes occur in them.

Finally, the favorable effects that are asserted by excellent observers (Kocher, Pineles, Biedl) to have followed the administration of thyroid substance in the postoperative tetany both of men and of animals must not be overlooked, for these favorable effects are in contradiction to the view that the thyroid and the parathyroid functions are antagonistic. The objection, that thyroid substance so fed owes its efficacy to some included parathyroid substance, is not valid, for the amount of the latter that could be present is too small to have any therapeutic effect. According to the estimates of Pineles, the thyroid of the sheep and of the calf contain only one part by weight of parathyroid to 309 and 379 parts respectively of thyroid; even 200 times the dosage of parathyroid that could be contained

in the thyroid administered yields no therapeutic effect. Postoperative tetany undergoes prompt improvement on treatment with thyroid substance. In experimental animals life is considerably prolonged by this medication, and Biedl urges that thyroid therapy should always be resorted to in postoperative tetany of human beings, in order to give time to any accessory parathyroid glands remaining to develop their full function.

In idiopathic tetany there are often signs of simultaneous disease of the thyroid; thus, von Frankl-Hochwart pointed out that, in chronic tetany, struma is often present (13 out of 26 cases). He also noticed that, in a few cases, mild myxedematous symptoms appeared in chronic tetany. Similar observations have been made by other clinicians, and it has been asserted that the administration of thyroid extract diminishes the trophic disturbances of tetany and causes the mononucleosis of the blood in that syndrome to disappear.

In the acute stage of tetany, or just after it has passed, signs of mild hyperthyroidism not infrequently appear (Falta and Kahn). It looks as though there were in many cases of tetany, during the acute exacerbations, a temporary increase in the activity of the thyroid, though, later on, in cachectic states, a mild degree of thyroid insufficiency develops.

Enough has been said to prove conclusively that a close relation exists between the functions of the thyroid and the parathyroid glands. The similar histological structure, the hypertrophy of one organ after extirpation of the other, the results of organotherapy above referred to, the tendency for disease in one organ to be accompanied by changes in the other, all attest to this. The evidence seems to me to support the idea of a reciprocal supporting function rather than that of reciprocal antagonism.

Hypophysis Cerebri

The hormonopoietic glands are so closely linked together into a chain that, when one endocrine gland is disturbed, we have learned always to look for disturbances in one or more of the other glands. There is as yet but relatively little, however, pointing to the hypophysis in tetany.

Certain observations suggestive of hypophyseal implication in tetany have nevertheless been recorded and may here be briefly referred to. Crises of polyuria, for example, sometimes occur in the course of tetany. They have been described by E. A. Locke of Boston (1902) and by Gatti (1910), and an analysis of the cases reported in the literature will show that polyuria has not infrequently been recorded as having been observed, especially during spontaneous attacks. This polyuria in tetany may be simply an evidence of vasomotor or secretory hyperexcitability, but the possibility of an associated disturbance of the pars intermedia of the hypophysis should be kept in mind, now that some believe in a relationship of the pars intermedia to the polyuria of diabetes insipidus.

Again, associated disease of the pituitary gland may be responsible for some of the psychoses of tetany. This possibility has been suggested by Barrett (1920), who observed two patients who exhibited a tetany psychosis during life and at autopsy were found to have cysts in the pituitary gland.

Furthermore, the effects of extracts of the pituitary gland in controlling tetany indicate a coöperative action between the hypophysis and the parathyroid glands. Ott and Scott (*a*) (1908) showed that in feline tetany, the pituitary gland, given in distilled water subcutaneously, had an effect at least equal to that of calcium salts in relieving the tetany that followed complete parathyroidectomy. Pal of Vienna (1909) gave pituitrin to a boy suffering from severe tetany, and reported that the syndrome disappeared in 24 hours.

Ott and Scott found, however, that pituitrin in feline tetany had only a fugitive action. They asserted, nevertheless, that neither pituitrin nor infundibular extract had as lasting effects as the whole gland was capable of exerting.

The hypertrophy of the pars intermedia of the hypophysis that follows extirpation of the parathyroids also speaks in favor of a coöperative relation between these two organs. Thus, Thompson found that the histological changes in the pars intermedia following parathyroidectomy are almost identical with those following thyroidectomy, the identity extending even to the marked accumulation of colloid. The evidence, therefore, favors the view that the hypophysis cerebri can, on demand, compensate to a certain extent for the loss of parathyroid function.

Chromaffin System

Some of the symptoms in the acute stage of tetany suggest that, in this syndrome, there is an increased activity of the chromaffin system. Certain of the phenomena met with in animal experimentation, too, point to the tendency to hyperchromaffinism in hypoparathyroidism. Guleke found that the tetany spasms disappeared in parathyrodectomized animals when he extirpated also the suprarenal glands. Even ligature of the suprarenal veins would temporarily cause the attacks of tetany to disappear, though, as soon as the circulation in the suprarenals became reëstablished, the attacks of tetany recurred. These experiments of Guleke are suggestive of an antagonism between the parathyroids and the suprarenals.

Some experiments made by Eppinger, Falta and Rüdinger on tetany animals suggest that the secretion of the parathyroids inhibits the sympathetic nerves, whereas that of the chromaffin system excites them. Other experiments by Falta and Kahn have convinced these authors that a hyperexcitability of the sympathetic nerve endings appears after parathyroidectomy, so that the injection of epinephrin causes a primary vasodilatation.

Since the evidence thus far adduced points to an antagonism between the functions of the parathyroids and those of the chromaffin system, the occurrence of symptoms of hyperchromaffinism in tetany need not surprise us.

Kocher of Berne, however, called attention, on the contrary, to the fact that marked pigmentation of the skin, and even bronzing of the skin, may develop after strumectomy in man, if the symptoms of tetany are prominent.

Pancreas

There is but little pointing to disturbances of the pancreas in association with tetany. Temporary alimentary glycosuria has, however, been observed in attacks of idiopathic tetany in human beings. In the experimental tetany of dogs, too, the capacity of the organism to assimilate glucose seems to be depressed. But Kojima (*a*) (1917) found that the addition of parathyroid substances to the daily diet of animals caused no histological changes in the pancreas; he examined the islands of Langerhans carefully, but could discover no alterations in them.

Gonads

The relations of menstruation, of pregnancy, and of lactation to tetany are among the well established facts connected with the subject; these conditions all predispose to the occurrence of tetany. Maternity tetany has been as well studied, perhaps, as any form of tetany. Evidently the demands made upon the parathyroid functions during maternity are often greater than can be met by the glands supplying the secretion. Whether or not these demands originate in changes in the gonads is a matter that has not yet been determined.

In experimental partial parathyroidectomy in animals the lessened parathyroid function that results may suffice for the ordinary life of the animal though not for extraordinary demands, for if pregnancy occur, tetany will develop. Iselin has made the further interesting observation that even the offspring of parathyroidectomized rats show a markedly increased electrical excitability of their motor nerves, and they are so sensitive themselves to parathyroidectomy that within from four to ten hours after that operation, presenting the phenomena of a violent tetany, they die. It is believed that this influence of the parathyroidectomized mother on her offspring is not transmitted through the germ plasm, but depends rather upon a diminution of the supply of parathyroid secretion to the fetus while it is within the uterus.

Experiments of Silvestri (*b*) (1910) had indicated that the previous extirpation of the gonads can prevent the tetany that otherwise will develop in thyroparathyroidectomized animals. These findings, however, have not been confirmed by subsequent investigators. Silvestri's experiments have

been repeated in dogs and in rabbits by Massaglia (1911) and by Clércet and Gley (*a*) (*b*) (1911), but the tetany could not thus be prevented.

Thymus Gland

On account of the laryngospasm that occurs in tetany, in rickets, and, sometimes, in status thymicus, the idea of a relationship of the thymus gland to tetany and to insufficiency of the parathyroid glands has arisen.

The most interesting experimental work in this connection is that of Uhlenhuth (*c*) (*d*) (*e*) (1918-19) done at the Rockefeller Institute in New York. This observer fed larvæ of the salamander *Amblystoma opacum* on thymus gland derived from the calf. The members of one series of half a dozen larvæ, otherwise untreated, all developed tetany with convulsions, which ceased as metamorphosis approached. After metamorphosis, all the larvæ of this series were free from tetany, though the limbs and feet remained deformed and contracted and the muscles were permanently paralyzed. A second series of larvæ was kept in a solution of calcium lactate and fed on thymus gland. Tetany was less marked than in the first series, but the residual paralyses and deformities were quite as marked; moreover, several weeks after metamorphosis, tetany appeared in members of this series. A third series of the larvæ was kept in a solution of magnesium lactate during the thymus feeding. These larvæ behaved like those in the second series, except that the tetany was still less marked during the larval period.

Further proof of the antagonism that he believes to exist between the thymus and the parathyroids has been brought by Uhlenhuth (*e*) in a second paper (1919). It seems that the larvæ of *Amblystoma opacum* have no parathyroids until metamorphosis occurs. If they be fed on calf's thymus while in the larval state, tetany, as has been mentioned above, develops. Uhlenhuth found, however, that after the development of their parathyroids, three of the animals fed on thymus gland were able to subsist for at least seven months without the appearance of tetany.

Uhlenhuth believes that the parathyroid glands are, in the salamander, as they are in man, important in the prevention of tetany. But, in addition to the parathyroids, the salamander, he asserts, possesses another mechanism that, during the larval period, prevents the development of the tetany that would otherwise result from the toxic effect of the larval animal's own thymus gland. In *Amblystoma opacum* and in *Amblystoma maculatum* this mechanism suffices for the prevention of tetany due to auto-intoxication by the animal's own thymus; whereas in *Amblystoma tigrinum* this same mechanism is capable of preventing tetany, even when to autothymo-intoxication is added the poison of calf's thymus fed to it.

Uhlenhuth points out that, if the thymus be regarded as the organ the activity of which is responsible in hypoparathyroid states for the appear-

ance of tetany, it is easy to understand why tetany is so much more common in children than in adults, since in the latter the thymus has been largely replaced by connective tissue. He suggests, too, that the relation of the thymus to tetany may explain the appearance of tetany during pregnancy, for, though the parathyroid secretion of the mother would suffice to neutralize the tetany threatening influence of the mother's largely atrophic thymus, it might not perhaps be equal to the prevention of tetany when her own thymus function is supplemented by thymus products entering her blood from the intra-uterine fetus.

The results of these experiments of Uhlenhuth, should they be confirmed by other workers, may prove to be of high importance for the understanding of the pathogenesis of tetany.

15. The Metabolism in Tetany

With the rise of interest in biological chemistry, studies of the metabolism in all kinds of pathological processes have become popular, and it is not surprising, therefore, that the results of a series of investigations upon end metabolism and intermediary metabolism in tetany (both human and experimental) should have already accumulated. Most of the studies thus far made in tetany have dealt with the protein metabolism, the creatin and creatinin metabolism, the carbohydrate metabolism, the mineral metabolism and the total metabolism in patients presenting the syndrome or in animals in which the condition has been experimentally produced; but relatively little attention seems to have been paid to the metabolism of nucleins and purins, of fats, of lipoids, or of vitamins in tetany.

An analysis of the results of these various metabolic studies on tetany indicates that, on the whole, the metabolic processes are accelerated. This might, perhaps, have been expected, in view of the general hyperexcitability of the visceral nervous system that is known to exist in tetany.

It is, of course, highly important that we should learn to understand, not only the chemical and enzymatic composition of the internal secretion of the parathyroid glands, but also the nature of the disturbances of the body's chemical processes that follow upon parathyroidectomy; for, once we have obtained an intimate knowledge of the constitution of the parathyroid secretion and of the effects upon metabolism of parathyroid insufficiency, we shall have gone far on the road towards a much desired goal, namely, a knowledge of the exact pathogenesis of tetania parathyropriva.

Protein Metabolism in Tetany

Studies of protein metabolism in tetany, aside from the demonstration of its acceleration with increased output of total nitrogen in the urine, have been pursued in three main directions: (1) the study of ammonia

production and ammonia elimination; (2) the study of the nitrogen partition in the urine; (3) the search for abnormal products of protein metabolism that could be responsible for the intoxication in tetany.

The Production and Elimination of Ammonia in Tetany.—That the ammonia of the blood and of the urine is increased in amount in many cases of tetany has been asserted by a number of investigators (Berkeley and Beebe (*a*), Frouin, Carlson and Jacobson, MacCallum and Voegtlin, Medwedew, J. B. Cooke (*c*), Falta and Kahn, and Morel), though other observers (Albertoni, Greenwald (*a*)) think that too much emphasis has been placed upon increased production and excretion of ammonia. Berkeley and Beebe pointed out the resemblance of the syndrome in tetany to that producible by ammonia intoxication; the symptoms of both can be ameliorated by the administration of salts of calcium or of strontium. Frouin suggested that tetany may be due to intoxication with carbaminic acid. Carlson showed that the livers of animals exhibiting tetany have less than normal power to destroy ammonia (in experiments in which the overliving liver was perfused with blood to which ammonium carbonate had been added), but subsequent studies by Carlson and Jacobson indicated that there is no increase in the ammonia of the blood of the dog during tetany attacks and that, moreover, essential differences exist between the true tetany syndrome and the syndrome resembling tetany that is produced by poisoning with ammonia.

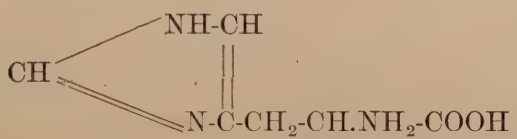
An increase of ammonia in the blood and in the urine seems to point to the catching up of ammonia out of intermediary metabolism, after the deamidization of the amino acids into which protein is degraded during digestion, so that the liver cannot make use of it in the formation of urea. Usually such a catching up of ammonia in intermediary metabolism is due to the existence of an acidosis. We have remarkable examples of this, not only in the acidosis of diabetes mellitus, but also in other forms of acidosis. Cooke was able to demonstrate the presence of lactic acid in the urine in parathyroidectomized animals at the times when the ammonia excretion was increased, an observation that has been confirmed by Morel, who also found that the lives of such animals could be definitely shortened by aggravating the acidosis through the administration of oxybutyric acid, or definitely lengthened by combating the acidosis through the administration of sodium bicarbonate. On the other hand, Grant and Goldman, working in Erlanger's laboratory in St. Louis, have been able to produce tetany attacks through deep breathing and found that these attacks were accompanied by an alkalosis. The careful metabolic studies of Isador Greenwald, of New York, revealed no increase of the ammonia of the blood after parathyroidectomy. He found a slight increase of ammonia in the urine, along with an increase of certain unidentified nitrogen products in the urine.

The Nitrogen Partition in the Urine in Tetany.—Studies of the nitrogen partition in the urine in the acute stage of tetany have shown that

(1) the total nitrogen is increased, (2) the ammonia ratio is increased (MacCallum and Voegtlin), (3) the amino acid fraction is usually normal, whereas (4) the peptid nitrogen fraction is considerably increased (Falta and Kahn). The increased output of peptid nitrogen, of total nitrogen, and of ammonia nitrogen apparently can continue for some time after the acute stage of tetany has passed.

Toxic Substances of Protein Origin in Tetany.—The possibility of the accumulation within the body of certain poisons derived from protein, especially from two of its constituent amino acids, histidin and arginin, has been suggested by the studies of several investigators.

Attention was drawn to *histidin* as the possible source of the tetany poison by the fact that the phenomena of tetany are similar to those of chronic ergotism (Fuchs (*a*)). The active principle of ergot seems to be beta-imidazolyl-ethylamin; and this substance is a derivative of one of the amino acid building stones of protein, namely histidin, which is beta-imidazol-alpha-amino-propionic acid:—



I should like to draw attention also to *arginin,* on account of the studies of Koch (*a*) (*b*) and, later, of Paton and his collaborators. Koch found certain amino bases (methylguanidin and trimethylamin) in the urine of dogs suffering from experimental tetany, and Paton and his coworkers assert that they can produce symptoms identical with those of tetany by the injection of guanidin and its salts. One probable source of guanidin in the body would, it seems to me, be the guanidino acid known as arginin, which is one of the diamino acids of the protein molecule. Arginin is alpha-amino-delta-guanidino-valerianic acid having the formula NH_2-C (NH)-NH-CH_2-CH_2-CH_2-CH.NH_2-COOH.

It may be that the further studies of these derivatives of histidin and arginin may throw much light upon the true nature of the tetany poison, though it is too early to be sure of this.

Creatin is another amino acid that contains a guanidin group, for it is methylguanidino-acetic acid, having the formula NH_2-C(NH)-N(CH_3)-CH_2-COOH. The anhydrid of creatin is known as creatinin, and this substance is methyl-glyco-cyamidin.

The guanidin of arginin is ordinarily converted in the body, through hydrolysis, into urea and ornithin (Drechsel), probably through the influence of a ferment, arginase, discovered by Kossel. Creatin and creatinin could, in a similar way, have their guanidin groups changed into urea by hydrolysis in the normal organism. Should the studies of Koch,

of Paton, and of others, who have found guanidin accumulations in the body in tetany be confirmed, I would suggest that, in autopsies on tetany patients, tests be made to see whether or not arginase is absent. Arginin has been found in the spleen (Gulewitsch) and it might be well to test the spleen and other organs for the presence or absence of arginase and similar guanidin transforming ferments; and, since the presence of healthy parathyroids prevents tetany, I would further suggest that the parathyroid glands themselves be examined for arginase, for it might very well be that these glands are the source of this ferment, and perhaps of other important catalytic agents.

Metabolism of Nucleins and Purins in Tetany

In connection with the metabolism of nucleins and purins, attention may be drawn to three sets of substances that have this source, (1) xanthin and its derivatives (guanin and caffein), (2) inosinic acid, and (3) phosphoric acid.

Xanthin and Its Derivatives.—It has long been known that xanthin and its substitution products belong to a group of convulsive toxins, which, acting upon the nerve centers rather than upon the peripheral nerves, cause muscular twitchings and rhythmical contractions, followed by paralysis. Berkeley and Beebe, thinking that these substances might impinge upon the same mechanism as the hypothetical toxin of tetany, made some experiments in the treatment of xanthin poisoning, in which they made use of remedies that are known to ameliorate the symptoms of tetany. They found that the toxic effects of intravenously injected xanthin can be very promptly relieved by the administration of salts of calcium and of strontium, though the betterment is not quite so prompt as is seen in the treatment of the symptoms of tetany by the same salts. Though Berkeley and Beebe did not suggest that tetany is due to poisoning by ammonia or by xanthin, these authors thought it probable that the poisoning in tetany may be due to some chemical substance of metabolic origin that acts in a way similar to that of xanthin. They inclined also to the belief that the parathyroid glands are concerned chiefly in furnishing enzymes that are of prime importance for the intermediary metabolism of nitrogen.

Xanthin, guanin, and caffein all contain a guanidin group, which could possibly be brought into relation with a guanidin intoxication of the body (*vide supra*). Guanidin of this source would have to be attributed to a disturbance of purin metabolism, rather than to an anomaly in the metabolism of proteins. Xanthin is converted into uric acid by means of a ferment known as xanthin oxydase. In human beings this ferment has been found in only one organ, namely, the liver. In animals it has been found in other organs also, especially in the spleen. Guanin is derived also

from guanosin, a nucleoside, which in turn is derived from the extranuclear mononucleotide known as guanylic acid.

Though the proof has not yet been brought that either xanthin or guanin is actually concerned in the production of the tetany intoxication, the possibility of the participation of one or of both substances in the process must, for the present, be kept in mind.

Inosinic Acid.—Inosinic acid, an extranuclear mononucleotide, is a forerunner of hypoxanthin. Greenwald for a time thought that inosinic acid might be a cause of tetany, but later abandoned the idea.

Phosphoric Acid.—Phosphoric acid may be derived from nucleic acid, but it has also other sources within the organism. Greenwald (*b*) (1916) reported that the diminished excretion of phosphorus is the most striking alteration of metabolism after parathyroidectomy, and suggested that a search for the form in which phosphorus is retained might throw some light upon the functions of the parathyroid glands.

Carbohydrate Metabolism in Tetany

In the literature of tetany several reports upon disturbances of carbohydrate metabolism can be found. Thus, Eppinger, Falta, and Rüdinger state that, in dogs deprived of their parathyroid glands, the glycosuric effect of epinephrin is increased, provided that the injection does not cause a general tetany spasm. Falta and Kahn have reported that, in human tetany, in the acute stage, they had never observed glycosuria after injections of epinephrin, though the epinephrin did cause an essential increase of the reaction of the cardiovascular apparatus. They thought that this dissociation of the epinephrin effect was due to several factors, most notable, perhaps, the increase of the use of sugar through the enormous vascular constriction that it produces. After the tetany had subsided they were able often to demonstrate a distinct glycosuric effect on epinephrin injection.

In tetany in dogs, Eppinger, Falta, and Rüdinger found the assimilation limit for glucose constantly depressed, though in tetany in man, tested by frequent examinations, this was not observable.

Marine (1914) found that removal of the parathyroid glands in dogs immediately lowered the alimentary tolerance for sugar, though rarely to the degree of constant glycosuria.

The total metabolism seems, in the acute stage of tetany, to be markedly increased. Studies of total metabolism should also be made in chronic tetany on account of the cachexia that develops in that condition. In general, it may be assumed that there is an increased mobilization and combustion of carbohydrates in tetany with increased heat production, though in favor of a contrary view Watanabe (1918) found a decrease in the blood

sugar in tetany; and he has maintained that, in rabbits, either the administration of guanidin or the removal of the parathyroid glands will cause a hypoglycemia.

Brown and Fletcher (1915), of Toronto, feel sure that tetany may be produced in children by high carbohydrate feeding, provided the carbohydrate foods have, in the course of their preparation, been heated to the boiling point or higher. Such improper feeding results, they believe, in a disturbance of the body salts. At the height of tetany there is, they assert, an almost complete retention of sodium and potassium (irritating salts) and a great loss of magnesium (sedative salt). As improvement of the child ensues, there is an increased flow of urine, accompanied by relief of the constipation; with the diuresis and the evacuation of the intestines, the stored up sodium and potassium salts are rapidly excreted. In 78 per cent of the cases they observed, the children that manifested the tetany were being fed upon proprietary or upon cooked foods, and 43 per cent of them developed tetany while being fed upon the former alone. In five of their patients tetany developed during a period when the food consisted entirely of bread and milk (see Fig. 10). Infants fed over long periods with food containing large percentages of carbohydrates (e. g., proprietary foods) are prone to the development of a water retention. Such infants, frequently spoken of as "water babies," show a great susceptibility to tetany, owing, Brown and Fletcher think, to the retention of sodium and potassium ions, which are direct excitants of the nervous tissues.

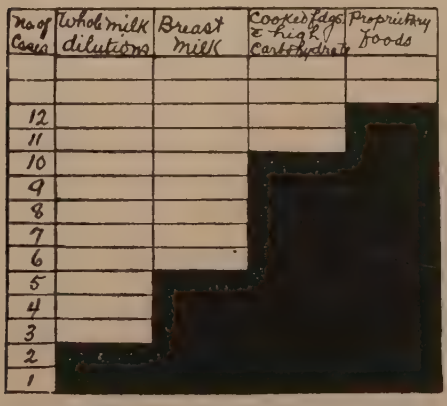


Fig. 10. Showing the relation of the number of cases of tetany to the previous feedings. (After Brown and Fletcher, Am. J. Dis. of Children, Chicago, 1915.)

Finkelstein (*a*) stated, as early as 1902, that cow's milk fed to infants causes a functional anomaly of intermediary metabolism that leads to increased electrical excitability of the motor nerves. This hyperexcitability, he asserted, does not develop when the diet consists of human milk, of vegetables, and of bouillon and egg.

Larsson, of Stockholm, in 1917 advanced the view that some crystalloid heat stable element in the whey of cow's milk is responsible for spasmophilia in children. According to the results of his experiments, the several constituents of milk albumin are incapable of producing spasmophilia, whereas whey alone, entirely free from albumin, will produce it.

The relations of carbohydrate metabolism to tetany are, as will be seen from the above reports, as yet far from clear. It is obvious that a series

of systematic studies must still be made in this field before any satisfactory conclusions can be reached.

Metabolism of Fats and Lipoids in Tetany

Aside from (1) the observations of increased total metabolism in tetany and (2) the observations on the occurrence of acidosis in tetany, I can find but little in the literature referring to the fat metabolism in this disease. The same may be said of the metabolism of lipoids in tetany.

Mineral Metabolism in Tetany

On the subject of the metabolism of mineral substances in tetany there is now a considerable literature. It would be tedious to pursue the studies that have been made in their minute and intricate details, but the essential points can quickly be summarized. The majority of the metabolic researches in tetany have dealt with (1) the disturbances of the acid base equilibrium and (2) the disturbances of kation balance that occur, notably with the deficiency, in the content of the blood and tissues, of calcium and magnesium ions (nerve sedatives), and with the coincident preponderance of sodium ions (nerve irritants). In infants the tendency to retention of water in the so-called "water babies," which are especially prone to exhibit the tetany syndrome, has raised, too, the general question of the behavior of water metabolism in parathyroid insufficiency. Though the kations in tetany have received much attention from investigators of metabolism, there has as yet been but little work done upon the behavior of anions in this disease, nor has the important matter of the interrelationships of electrolytes to colloids in tetany been the subject of the study that it merits.

Calcium and Magnesium.—Sabbatani (1901) observed that calcium salts are antagonistic in their effects on the animal organism to sodium citrate, and made experiments that proved, by applying the salts directly to the surface of the brain, that these effects concern especially the irritability of the nervous system. Calcium chlorid solutions reduce the mechanical and electrical excitability immediately, whereas sodium citrate and sodium oxalate have an opposite effect. The latter salts greatly increase the excitability of the nervous system, so that the stimuli necessary to produce muscular movements are markedly decreased. Calcium applied after sodium will neutralize the effects of the latter. As an inference from his experiments, Sabbatani suggested that calcium might be useful in the treatment of epilepsy.

J. Loeb, in 1902, showed that the injection into the animal body of any salt that precipitates calcium results in the development of muscular twitchings. He suggested that, in disease abnormal conditions, in which an increase of such acids in the circulation could diminish the amount of

calcium in the body, might easily arise, and that the necessary outcome would be muscular twitching. He pointed out that, in such instances, the administration of calcium salts might be expected to relieve the symptoms and, perhaps, cure the disease. He further stated that to suppress neurogenic twitchings, more calcium might be required than the amounts found necessary to suppress myogenic twitchings.

J. B. MacCallum, in a series of important papers published between 1903 and 1906, showed that hyperexcitability in the domain of the visceral nervous system can be aroused by the injection of certain salts that have an action antagonistic to that of calcium, and that the symptoms resulting can be suppressed by the addition of a soluble calcium salt to the solution injected.

These several observations, made by workers in general physiology, were destined to influence in a directive manner the subsequent researches of clinicians who studied the hyperexcitability of the motor nervous system in tetany.

As is often the case, the observations of the experimental physiologists found a certain corroboration in the studies of clinicians, whose researches were made entirely independently. Thus, Thiemich (*b*) (1903) stated that spasmophilia is most common in artificially fed children and suggested that cow's milk is especially likely to bring on the condition, a view that was supported by the observations of Japha and of Finkelstein. Stöltzner believed that this effect of cow's milk is due to excessive retention of calcium in the tissues, and attributed tetany and spasmophilia to a sort of calcium poisoning. But subsequent clinical investigators could not confirm Stöltzner's view; they demonstrated that, on the contrary, there is a calcium deficiency in the body in tetany. Thus Quest in 1905 found that the calcium content of the brain is remarkably lowered in spasmophilia, and both he and Silvestri, who confirmed his findings in 1906, suggested that tetany is due to hypocalcification of the nerve centers. In still later papers Quest was able to show that calcium-poor food, fed to young dogs, increased the electrical excitability of their motor nerves, and further that, if calcium excess were experimentally produced in the tissue juices of animals, no increase, but rather a diminution, in the electrical excitability of the nervous system resulted. Silvestri, in 1906, called attention to the calcium deficiency that is met with in certain accidents of the puerperium (tetany, eclampsia). And Netter (*a*) (1907) observed a favorable effect from the administration of calcium salts by mouth in three cases of manifest tetany in children. This author emphasized the impoverishment of the blood and tissues in salts of calcium in diarrhea, in intoxications, and in lactation in adults, and in the period of growth in children. He stated, too, that the classical association of tetany and rickets brings to mind the probability of lime insufficiency.

A number of other papers published at about this period dealt also with

the calcium question, but general interest in the subject of the relation of tetany to calcium metabolism was excited by the important paper of MacCallum and Voegtlin, published in 1909. In their article, these American investigators expressed the opinion that the withdrawal of calcium from the nerve cells leaves them in a state of hyperexcitability, which can be made to disappear by supplying the body with a solution of calcium salts. Tetany, they asserted, may be regarded as an expression of hyperexcitability of the nerve cells, due to some such cause as calcium deficiency in the nerve cells. They found that the injection of a solution of a salt of calcium into the circulation of an animal exhibiting the symptoms of tetany promptly checks all these symptoms and restores the animal to an apparently normal condition. They asserted further that injections of magnesium salts have a similar effect, though the effect is masked to some extent by the toxic action of these salts. The injection of solutions of salts of sodium or potassium, even of the alkaline salts of sodium, on the contrary, intensifies, according to MacCallum and Voegtlin, the symptoms of tetany. As a result of their own studies and of the studies reported in the literature, these authors felt convinced that there is a marked reduction in the calcium content of the tissues, especially of the blood and brain, in tetany and that there is an increased output of calcium in the urine and feces when the syndrome develops. MacCallum and Voegtlin further pointed out that, though the signs of acidosis are present in the urine in tetany, the symptoms of tetany are not ameliorated by the injection of alkaline sodium salts into the blood. The acidosis may, they thought, be important in draining the tissues of calcium salts. The same investigators also asserted that the parathyroid secretion must in one way or another control the calcium exchange in the body, and suggested that, in the absence of normal amounts of parathyroid secretion, there may be formed certain chemical substances that, combining with calcium, abstract it from the tissues and lead to its excretion. The presence of normal amounts of the parathyroid secretion prevents, they believed, the appearance of such substances. Though they could not determine the mechanism when the action of the parathyroid secretion is lost, its results (namely, the impoverishment of the tissues with respect to calcium and the subsequent development of a hyperexcitability of the nervous system in tetany) they believed to be proven. And they surmised that the same explanation could be applied to the pathogenesis of spontaneous tetany in human beings. In this, as in experimental parthyroidectomy, there must be a drain of calcium for physiological purposes, or, at any rate, there must be in it some condition that results in a withdrawal of calcium from the nerve cells. They suggested that, in this spontaneous tetany of human beings, the parathyroid gland may be only relatively insufficient, but the hypoparathyroidism probably accounts for the calcium drain.

These views of MacCallum and Voegtlin seemed not to be out of ac-

cord with the studies of Erdheim and those of Leopold and von Reuss. Erdheim's studies of rats after parathyroid extirpation had revealed, as we have already seen, hypoplasias of the enamel that indicate an anomaly of the calcium metabolism. Leopold and von Reuss (1908) found no marked diminution in the total calcium in parathyroidectomized rats, but the total amount of calcium in the bodies of growing rats suffering from tetany was definitely less than in the bodies of healthy animals, and, furthermore, the relation between the bone calcium and the calcium of the soft parts was always lower than in control animals, for the soft parts were richer in calcium, the bones poorer in calcium than normal, an observation that seemed to be in accord with the histological findings in the bones and in the teeth. These authors conclude, therefore, that there is, in tetany, a diminution of *active* calcium in the body.

Since the papers of A. Netter and of MacCallum and Voegtlin, many authors have reported success in the treatment of tetany by the administration of calcium salts (Berkeley and Beebe, Ott, Bell and Martin, Stone, Roger Morris, Howland and Marriott), though most admit, however, that in many cases the calcium salts have only a temporary effect. If the parathyroid insufficiency does not become compensated for, the tetany continues and may be fatal. Biedl could not prolong the lives of cats by the administration of calcium after removal of the thyroid and parathyroid glands.

Moreover, the salts of calcium possess no monopoly of favorable influence, for the salts of magnesium and the salts of strontium exert a very similar effect upon the symptoms of tetany (Canestro). Even the salts of lanthanum and of thorium are said to diminish the number and intensity of the attacks of muscle spasm in tetany (Frouin). And Joseph and Meltzer (1911) found that the intravenous injection of a sodium chlorid solution in molecular concentration in amounts of from 10 to 20 c.c. per kilogram, stopped the hyperkinetic symptoms of tetany immediately and permanently in parathyroidectomized dogs; but the animals died, nevertheless, within two weeks, of cachexia (without spasms). Meltzer's studies are of great interest when we consider the views of Sabbatani and of Loeb regarding the influence of disturbances of the kation balance in the body.

In recent years a number of studies of calcium metabolism in human and in experimental tetany have been undertaken by American investigators. Thus, J. V. Cooke, influenced by the publications of MacCallum and Voegtlin and of Underhill and Saiki, undertook to determine (1) whether or not an increased excretion of calcium during tetany would become more apparent if animals were kept on a calcium-poor diet for long periods, and (2) whether the increased salt elimination described is confined to salts of calcium or includes also salts of magnesium. Cooke observed, therefore, (1) the excretion of calcium and magnesium in normal

animals, some of which were kept on a diet of constant composition, others of which were starved, and (2) the excretion of calcium and magnesium in animals kept for a time on a diet of constant composition, after which a fasting period was instituted, during which the parathyroid glands were removed. Cooke asserted that the results of these experiments do not support the views of MacCallum and Voegtlin on the control of calcium metabolism by the parathyroid glands, and hinted that the function of the parathyroideal secretion is to oxidize certain of the intermediary products of protein catabolism; should the oxidation fail to occur, owing to parathyroid insufficiency, there is an accumulation of acid products that combine with ammonia and with other bases (calcium, magnesium), increasing the content of the urinary excretion in these kations. Cooke found that calcium, intramuscularly injected in tetany, was, in one instance, excreted in the feces rather than in the urine.

Haskins and Gerstenberger (1911) studied the calcium metabolism in a female negro infant, aged 14 months, in which they saw no benefit from dietetic treatment, or from the administration of calcium lactate or of desiccated ox parathyroid. They placed this child on a constant diet of milk and water for two months, during which time the body weight continued unchanged. During the metabolism experiment the child was kept on a Bradford frame. Though in normal children there is a calcium retention (more on a diet of breast milk than on a diet of cow's milk), they found in the tetany child a diminution of calcium retention. Schwarz and Bass[1] (1912) found no diminution of calcium retention in their case of infantile tetany, though they admitted that the calcium retention increased in their patient as the tetany disappeared, thus confirming an earlier observation by Cybulski, who in a seven months old child had found a far less marked calcium retention during attacks of tetany than at times when the infant was free from tetany symptoms.

MacCallum and Voegtlin (1913) found that, if, in experimental tetany, the animal be bled and the blood be replaced by an isotonic solution free from calcium, the tetany ceases and the excitability of the motor nerves is lowered, probably owing, they thought, to a general disturbance of the nutrition of the nervous system. The rapid introduction of oxalate-like substances into the circulation caused no change in the excitability of the nerves. They analyzed the blood in the tetany animal and found a relative poverty in calcium, as contrasted with control blood from a normal animal, but the administration of extracts of parathyroid glands did not increase the calcium content of the blood. Moreover, in partial parathyroidectomy, if the parathyroid insufficiency were not great enough to produce tetany, the calcium content of the blood remained within normal limits. Nevertheless, these authors maintained that the theory that tetany is dependent upon a disturbance of the calcium content of the blood is supported by stronger evidence than any other idea thus far advanced;

they admitted, however, that much work remained to be done before a clear conception of the process could be reached.

In contrast with these findings of MacCallum and Voegtlin are those of Neurath. Determining the calcium compounds that can be precipitated by oxalate rather than the total calcium, this observer found an increase of the calcium of the blood both in infantile tetany and in animals after parathyroidectomy.

Marine (1914), who studied parathyroidectomized dogs, found that the administration of calcium salts exerted a striking palliative effect upon the resultant tetany; though this treatment might tide over an otherwise fatal case, it was in no sense curative, and the way in which the calcium acted was not clear to him.

Bergheim, Stewart, and Hawk (1914) studied carefully the calcium metabolism in a negro, from whom the entire thyroid gland together with the parathyroid glands were of necessity removed on account of a malignant growth that required also laryngectomy. Tetany did not occur. Though the patient was given a diet rich in calcium, they thought that this alone could scarcely account for the non-appearance of tetany for a whole month; it seemed more likely that the man's organism had adapted itself gradually to parathyroid insufficiency during slow reduction of the parathyroid function by the neoplasm before the operation. They found a low calcium excretion in the urine (average excretion of 0.0134 gram per day on a daily ingestion averaging 1.6736 grams of calcium oxide) and a slight increase of the calcium content of the blood. They suggested that the calcium rich diet and a compensatory action of the hypophysis cerebri may have been contributing factors to the inhibition of tetany in this patient.

Certain recent studies of infantile tetany confirm, in opposition to Stölzner, the view that the calcium content of the serum is reduced. Howland and Marriott (1918) assert that in their cases of tetania infantum the amount present was only about 5.6 milligrams per 100 cubic centimeters, whereas in the normal child the amount is 10 or 11 milligrams. These observers could promptly relieve the symptoms of tetany by the administration of calcium.

In human tetany in adults due to overventilation, Grant and Goldman found, on the other hand, constantly no diminution in the calcium content of the serum, but rather a slight increase. They do not deny, however, the possibility that calcium may play a rôle in the production of the tetany of forced respiration. It is known that a decrease of CO_2 in the blood results in the precipitation of calcium (Barille, Marriott). Though the centrifuge revealed no precipitated calcium, Grant and Goldman suggest that very minute particles may have been held in solution by colloids and that there was a loss of active calcium.

When we survey the studies of calcium metabolism in tetany as a

whole, we arrive at the conclusion that the main fact thus far established is the diminution of the contents of the tissues, especially of the nervous tissues, in calcium, due probably to calcium withdrawal by acid bodies that tend to accumulate when parathyroid insufficiency occurs. An alkalosis may also, sometimes, diminish the available active calcium. The exact explanation of the vice of intermediary metabolism that causes the acidosis or the alkalosis is as yet wanting, though the latter may be due in some cases to overventilation (Grant and Goldman), in others to sodium bicarbonate intravenously administered (Harrop; Howland and Marriott).

Potassium and Sodium.—Many of those who lay emphasis upon the calcium deficiency of the nerve tissues in tetany believe that the hyperexcitability that accompanies it is due to the irritating effects of potassium ions, sodium ions, or both, that remain "unbalanced." On discussing carbohydrate metabolism in tetany (*vide supra*), the opinion of Brown and Fletcher is that proprietary foods and superheated carbohydrate foods when fed to infants cause tetany by disturbing the balance between the "sedative" and the "irritating" kations. Indeed, these authors would seem to ignore the parathyroid entirely as a factor in the tetany of childhood, though it is not improbable that, in this syndrome, parathyroid insufficiency and disturbed kation balance may be in some way linked together.

Loeb's studies showed that calcium ions depress neuromuscular excitability, but they also indicated that the muscles lost their excitability entirely if sodium ions were withdrawn from them. Rhythmical contractions of skeletal muscles occur when sodium ions and calcium ions are present in concentrations that lie within certain definite limits. Salts of magnesium can, like salts of calcium, inhibit the stimulating effects of solutions of sodium chloride. The results obtained by Joseph and Meltzer in the inhibition of tetany symptoms by the injection of solutions of sodium chloride were referred to above.

J. B. MacCallum proved that kations of the alkali metals exert an important influence upon the neuromuscular mechanisms concerned in intestinal peristalsis. Thus, peristalsis could be inhibited by salts of potassium and it could be increased by solutions that precipitate calcium.

Biedermann (1898) observed that the heightened excitability produced in muscle by sodium chloride solution is greatly increased by the addition of Na_2CO_3, Na_2SO_4 or NaOH. He was inclined to attribute the increase to a specific effect of the sodium ion.

The therapeutic administration of solutions of sodium bicarbonate has been known to call forth attacks of tetany. Thus Howland and Marriott (1918) report three instances in children, and Harrop (1919) reports an instance in an adult.

Obviously, attention in tetany should be directed from now on not only towards the kations of calcium and magnesium salts but also towards those of potassium and sodium salts.

Phosphoric Acid.—As was pointed out above, the behavior of anions in tetany has been but little studied. An exception may be made in the case of the anion of phosphoric acid, the excretion of which has been studied by Greenwald and by Schabad.

According to Greenwald, a diminution in the phosphate excretion is the most striking metabolic abnormality after parathyroidectomy, though just how the phosphorus is retained in the body he was unable to determine.

The studies of Schabad have thrown some light upon the phosphorus metabolism in tetany and in rickets. This observer has asseverated that the metabolism in rickets and that in rickets complicated by tetany are identical as far as calcium and phosphorus are concerned. In both conditions he found for calcium a diminution of retention with abundant excretion through the feces, and for phosphorus a marked preponderance of the excretion through the feces in contrast with that through the urine. Administration of phosphorus and cod liver oil caused, Schabad states, an amelioration of symptoms in both rickets and tetany.

Benger (1917) showed that tetany could be produced in dogs by intravenous injection of sodium phosphate in a certain quantity and of definite acidity, though if the H-ion concentration were greater than pH_6 tetany did not occur. The tetany was probably not due to the anion, however.

Water.—The so-called "water babies" are especially prone to exhibit the phenomena of spasmophilia, including tetany. According to the metabolic studies of Almon Fletcher and the clinical studies of Brown and Fletcher, improvement in infantile tetany sets in with diuresis and the overcoming of constipation. The relation of the water retention in such water babies to chloride retention should be carefully studied.

Vitamins in Tetany

Nowhere in the literature have I found any reference to the possible relation of vitamins to tetany. Certain points that may have a bearing upon the subject, however, seem to me worthy of mention. I refer especially to the prevalence of tetany in children that are fed largely upon proprietary foods, upon cow's milk alone, or upon any dietary that contains a high percentage of carbohydrates and especially of superheated carbohydrates.

The newer studies of vitamins (McCollum) indicate their presence in milk products, in leafy green vegetables, and in fruit juices. These vitamins are of different sorts; all of them appear to be necessary for the growth and general welfare of the body. It is conceivable, therefore, that injudicious diet, especially in children, may, through vitamin deficiency, be a factor in releasing tetany in patients predisposed toward it from insufficiency of the parathyroid glands. But no positive statement on this point dare be made until the proof has been sought and brought.

IV. The Etiology and Pathogenesis of Tetany with Comments Upon Its Different Forms

When considering the etiology and pathogenesis of tetany, it is helpful to consider the various forms of the syndrome that are met with in children and in adults. Cases of human tetany in adults were, from the etiological viewpoint, divided by von Frankl-Hochwart into several groups. Tetany presents certain peculiarities in each of these groups, and to these special features we shall immediately refer.

1. Idiopathic Tetany

(*Tetany of Workmen; Epidemic-Endemic Tetany*)

Idiopathic Character.—This group is characterized by its idiopathy. Spontaneous attacks of tetany appear in young, apparently healthy persons, and without any ascertainable cause.

Year	January	February	March	April	May	June	July	August	September	October	November	December	Total
1880	2	3	2	4	2	1	—	—	—	—	1	—	15
1881	—	4	6	1	3	2	—	—	—	—	1	3	20
1882	2	5	5	1	3	—	—	—	—	3	—	—	19
1883	6	6	13	8	4	2	—	1	—	—	1	3	44
1884	1	2	5	7	6	2	1	—	—	—	—	2	26
1885	1	2	4	4	3	2	1	—	—	1	1	2	21
1886	3	11	17	9	5	—	—	2	—	—	1	—	48
1887	4	2	9	4	—	2	—	1	1	1	5	3	32
1888	2	5	3	5	1	1	—	1	1	—	—	—	19
1889	4	4	2	5	1	—	—	—	1	—	—	3	20
1890	4	1	3	6	1	4	1	—	—	—	—	3	23
1891	4	2	2	3	1	1	—	—	1	—	1	—	15
1892	6	4	1	4	—	—	1	—	—	—	—	1	17
1893	2	1	3	5	—	2	—	—	—	—	—	—	13
1894	1	1	3	3	1	—	—	—	—	—	1	1	11
1895	3	3	9	6	2	—	1	—	—	—	—	1	25
Total	45	56	87	75	33	19	5	5	4	5	12	22	368

Fig. 11. Table giving the incidence of tetany by months and years. (After L. von Frankl-Hochwart.)

Seasonal Influences.—The attacks occur at certain times of the year, particularly in the early spring. Residents of cities in which tetany is endemic are prone to the attacks, and when the cases are numerous, owing to seasonal influences, "tetany epidemics" are spoken of. In Figs. 11 and 12 graphic representations of the numbers of tetany patients admitted to the General Hospital in Vienna from the year 1880 to 1895 (inclusive) are exhibited according to months. It will be noticed how few cases occurred in the months of August, September, and October, and what a

large number of cases were seen during the periods extending from January to April, inclusive, the acme of incidence being reached in March.

Epidemic Character.—The incidence of tetany in Vienna seems to have varied much in different years. Thus, in 1886 there were 44 cases and in 1883 about the same number, but in the year 1882 there were only 19 cases. Then the numbers fell to 32, 19, 20, 23, 15, 17, 13 and 11 per year. In 1895 there was another rise in incidence, the number for that year being 25. It is obvious, therefore, as von Frankl-Hochwart points out, that the curve is characteristic of the movement of an epidemic; for this is evidenced, not only by the rapid rise of the curve in March and April of each year, but also by the variations in frequency in the different years.

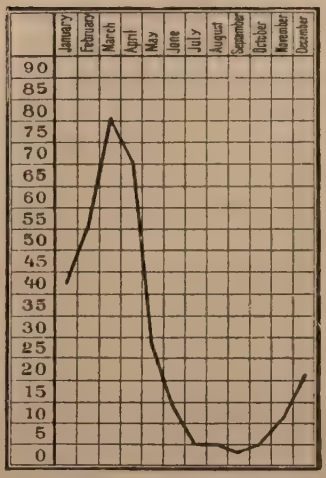


Fig. 12. The graph shows the number of tetany admissions (1880-1895) admitted to the General Hospital in Vienna, according to months, in the years 1880-1895. (After L. von Frankl-Hochwart.)

Sex.—In this epidemic form of tetany it is the males that are almost exclusively affected. It is in reality rare for women to contract this form of the disease. Thus, von Frankl-Hochwart observed that the lists included 399 males and only 19 females.

Occupation.—Von Frankl-Hochwart analyzed the patients also according to occupation, and found that among the men shoemakers and tailors predominated, though carpenters and joiners were also numerous; among the women seamstresses were the most numerous. It is evident, therefore, that certain occupations predispose to the idiopathic form of tetany.

It was further found that, in Vienna, persons of the better classes were scarcely ever affected by epidemic tetany.

Age.—As to age, it is the young men between 16 and 25 who are chiefly affected. Young men of these years make up 83 per cent of all the patients. Among women, too, the disease was more prevalent between the ages of 15 and 35 than at other ages.

In other words, von Frankl-Hochwart's analyses show that, in Vienna, tetany epidemics occur, which appear chiefly in March and April and which affect chiefly male shoemakers and tailors, rarely females (seamstresses) between the ages of 15 and 25 years.

Distribution.—The geographical distribution of idiopathic tetany is very interesting. In Germany, Heidelberg has many cases and Berlin only a few. Paris has reported, from time to time, the occurrence of many cases. In America spontaneous tetany is relatively rare. In 1894 J. P. Crozier Griffith brought together some 72 clinical records from this coun-

try. Idiopathic tetany seems to be relatively uncommon in the United States, in England, in Scandinavian countries, and also in Russia.

Familial Occurrence.—Familial idiopathic tetany has been frequently observed both in Europe and in this country. Thus Vaughan, in 1893, saw five children affected by the disease in one Italian family in New York. Chronic idiopathic tetany of the familial type has been described by Schiffer (1911).

Laureati (1916) advised the use of thyroid treatment to ward off or to cure the syndrome in families subject to tetany.

Recurrences.—Patients who have suffered from idiopathic tetany in one year are liable to recurrences in later years, especially in the spring.

Formes frustes.—At times of tetany epidemics, many persons who are apparently quite healthy and who suffer from no spontaneous tetany attacks, may exhibit, when carefully tested, a positive reaction to some single tetany sign (Trousseau's, Erb's, or Chvostek's sign).

Etiological Hypotheses.—Fuchs believes that idiopathic tetany is, in reality, a mild form of chronic ergotism, due to the use of rye bread, and tries to correlate the geographic distribution of tetany with the areas in which rye is much used instead of wheat. He points out, too, that the patients attacked by idiopathic tetany are persons who are more likely to use rye bread than the more expensive wheat bread. They are, in Vienna, often people who work at home, who do not during the whole week leave their workshops, and who always get the same cereals, apparently from the same small bakeries. Fuchs even goes so far as to ascribe the tetany of children and maternity tetany to the use of rye bread. He has further supported his doctrine by animal experiments, in which ergot was fed. The hypothesis, though interesting, has not as yet been verified.

In criticism of this view advanced by Fuchs, one may ask the question, Why is tetany so prevalent in Vienna and Heidelberg and so rare in other parts of Austria and in Germany, in which rye bread is fully as much used?

A second hypothesis associates idiopathic tetany in one way or another with goiter, which, as is well known, is distributed in certain definite geographic areas. From his studies of tetany and of goiter in India, especially in the Gilgit Valley, R. MacCarrison has advanced this view.

Certain exciting causes of the spontaneous attacks of idiopathic tetany have been mooted. In tetany epidemics, the patients, before the onset of the contractures, usually complain of paresthesias in the extremities, the actual spasms appearing only under the influence of some accident, such as a bad cold, sore throat, or other mild infection, some gastro-intestinal disturbance, or a mechanical or psychic trauma. In many cases, however, no such special precipitating cause is recognizable.

Many of the young workmen affected by seasonal tetany are found, on inquiry, to have suffered in early childhood from laryngospasm or from

convulsions, indicating the existence in them of spasmophilia in childhood. It would be interesting, in view of Uhlenhuth's ideas, to know how many of them, if any, have presented evidences of a status thymicolymphaticus.

It is said that patients among the working classes in Vienna suffering from idiopathic tetany, get rid of their tetany symptoms in one or two days if they are admitted to a hospital.

2. Tetany in Diseases of the Digestive Tract

At least four groups of cases of tetany occurring in association with diseases of the digestive tract have been described in the literature:—(1) Cases of gastric tetany; (2) cases of tetany in duodenal dilatations; (3) cases of colonic tetany; and (4) cases of tetany in association with helminthiasis.

Gastric Tetany (Tetania gastrica)

Kussmaul (*a*) (1869), in his article on the treatment of dilatation of the stomach, reported the occurrence of tonic spasms (tetany) in association with marked gastric dilatation. This form of tetany was especially well studied by the French observers Bouveret and Dévic (1892), and by Fleiner (1900 and 1903). Karl Wirth has collected all the cases published up to 1910 and has subjected them to a critical analysis.

In the majority of cases of gastric tetany reported, there was marked dilatation of the stomach, due to pyloric stenosis. This form of the disease occurs generally in older people and shows a high mortality. Medical treatment is unsuccessful, though surgery is curative, if the stenosis be benign.

Among the *benign gastric stenoses* observed in association with tetany may be mentioned (1) stenosis due to scar from old ulcer of the pylorus or of the duodenum, (2) that due to hourglass stomach with marked dilatation of the part proximal to the constriction, (3) that due to peripyloric adhesions, (4) that due to obstruction of the pylorus by foreign bodies, and (5) hypertrophic stenosis of the pylorus. The *malignant stenoses* have been mainly carcinomatous in origin, though occasionally round cell sarcoma was the cause of the obstruction at the pylorus.

Only a relatively small number of the hosts of patients with gastric dilatation ever develop tetany. A disposition to tetany must therefore be assumed in addition to the stenosis. According to the current view, a parathyroid insufficiency exists and toxins absorbed from the dilated stomach further injure the parathyroid glands or interfere with the exertion of their normal influence and thus call forth the tetany. If this view be correct, gastric tetany would fall in the larger group of cases of tetany due to intoxications.

Recently, the attempt has been made to explain gastric tetany on the

basis of a disturbance of the acid base equilibrium in the body. Thus, McCann (1918) suggested that the tetany may be due to an alkalosis that results from a disproportion between the rates of secretion of acids and alkalis by the gastro-intestinal tract. In pyloric stenosis the gastric acid does not pass into the duodenum to excite the intestine to secrete its alkaline secretion, and this might be expected to lead to an excess of basic substances in the blood. MacCallum's experiments (1920), referred to elsewhere in this article, point in a similar direction.

Tetany Due to Stenosis of the Duodenum

Some five cases of tetany of supposed duodenal origin are on record. In that reported by Fenwick Young (1902) the stenosis of the duodenum was due to adhesions. In the case of Blazitek (1894) the obstruction was caused by a tumor of the gallbladder. Two cases of duodenal obstruction with tetany have been associated with tumor of the pancreas and one with retroperitoneal hematoma. In the case described by Barker and Estes a so-called "idiopathic dilatation of the stomach and duodenum" existed and was associated with familial hematoporphyrinuria and tetany. The so-called idiopathic gastric-duodenal dilatation probably falls in the group known as "gastromesenteric ileus."

Tetany in Colonic Dilatation

In 1907 Longleaf, of London, described four cases of colonic tetany. Dilatation of any part of the gastro-intestinal tract, with obstruction and absorption of the contents of the tube, may, apparently, give rise to tetany in predisposed individuals.

Tetany in Helminthiasis (Worm Tetany)

According to Deplaigne tetany in the adult may occur in association with invasion by intestinal worms. In 1874 Riegel reported a case of tetany associated with tapeworm (Tænia mediocanellata) in the intestines. A careful search for tapeworm in tetany patients in Vienna, where the disease is common, was, however, fruitless.

Greenfield (1903) reported a fatal case of tetany associated with tapeworm (Tænia mediocanellata) in the intestines.

3. Tetany in Association with Infectious Diseases

The occurrence of tetany has often been observed in association with acute and chronic infections. Though in the literature mention is made

of a large series of infections, it is in typhoid, measles, influenza, tuberculosis, pneumonia, and acute articular rheumatism that the complicating tetany has most frequently been seen. In many of these instances, however, the patients had suffered from attacks of tetany earlier in their lives. Moreover, tetany in association with infections occurs most often during the tetany months and among people who reside in tetany towns. It would seem very clear, therefore, that the infection with which the tetany is associated is merely the exciting cause of an outbreak of tetany in a patient who already suffers from the disease in a chronic or in a latent form.

In favor of this view several facts may be adduced. Thus, the observations of Chvostek junior (1907) showed that, among patients who had had tetany and were in the period of remission, an attack could be precipitated by the administration of old tuberculin. Eppinger has suggested that possibly the poison of tuberculosis contains a component that has a specific injurious effect upon the parathyroid glands, just as many assume that the poison of tuberculosis also specifically affects the adrenal glands. The frequent occurrence of Chvostek's sign in severe tuberculosis has been repeatedly emphasized. The occurrence of tetany in the course of miliary tuberculosis, however, may be due to the presence of miliary tubercles in the parathyroid glands themselves, as has been demonstrated by Milton Winternitz.

4. Tetany in Association with Intoxications

What has been said concerning tetany in association with infections holds also for tetany in association with intoxications. The intoxication must be looked upon as a releasing cause in persons who are predisposed to tetany by an already existent parathyroid insufficiency or some other predisposing condition. Among the intoxications that have been especially noted in connection with tetany may be mentioned those due to alcohol, to morphin, to phosphorus, to chloroform, to lead, and to ergot. Tetany in connection with nephritis and uremia has also been described as an intoxication tetany.

5. Tetany Associated with Menstruation, Pregnancy and Lactation (Maternity Tetany)

Von Frankl-Hochwart was able to collect seventy-six instances in which tetany was associated with pregnancy or with the period subsequent to it. In twenty-eight of these cases, the tetany appeared between the sixth and the eighth month of pregnancy. In nineteen of the cases it occurred

post partum, in twenty-nine during lactation. A portion of these patients had earlier been operated upon for goiter. Some of the pregnancy patients suffered from convulsive seizures, causing premature delivery, after which the tetany ceased. When the tetany continued and lasted for some time, trophic changes were common (falling out of the hair, cataract formation). Children born at term of tetany mothers often exhibited tetany also, either immediately after birth or later on.

As has already been pointed out, maternity seems to throw an especial burden upon the parathyroid glands, and parathyroid insufficiency easily develops during the process. Even menstruation may be the cause of the development of tetany, or an existing tetany may, in its course, be aggravated by the occurrence of menstruation.

Maternity tetany is much more common in the spring months than at other times, and in tetany towns than in other places.

6. Tetany after Operations for Goiter (Tetania strumipriva)

Tetania strumipriva, so important for the development of our knowledge of the relation of the parathyroid glands to tetany, is one of the severest forms of the disease, often ending fatally. We have outlined above (see Historical Notes) the history of the development of our knowledge of this form of tetany. It is one of the brilliant chapters in endocrinology.

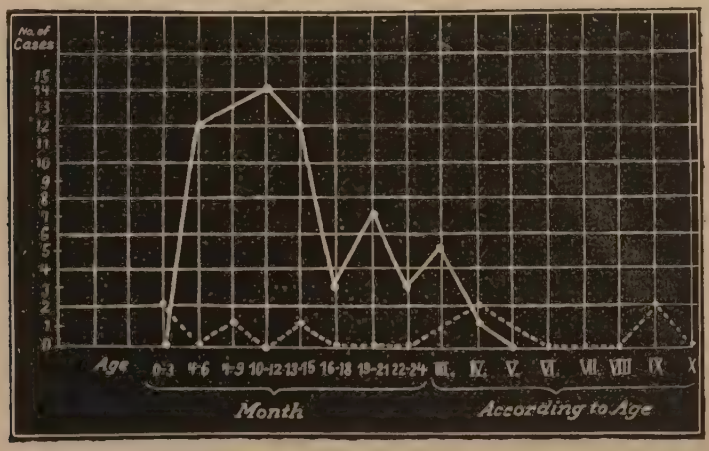
Tetany after operation for goiter, thanks to our newer knowledge, is growing ever less common. Not only are the parathyroid glands now left behind at the operation for goiter, but the technique of the operation is being ever improved, so that injuries to the parathyroid glands from pressure, from hemorrhage, from cutting off of the blood supply, and from scar formation, subsequent to operation, are, as far as possible, avoided. Cases of tetania strumipriva still occur occasionally, however, even in the hands of the best operators. Should a surgeon by mistake, or by unavoidable accident, remove one or more of the parathyroid glands, or should the operation be so extensive (on account of carcinoma) that the parathyroids must be removed, they should, if not actually invaded by the neoplasm, be immediately retransplanted, while the patient is still under the anesthetic.

7. Tetany in Children

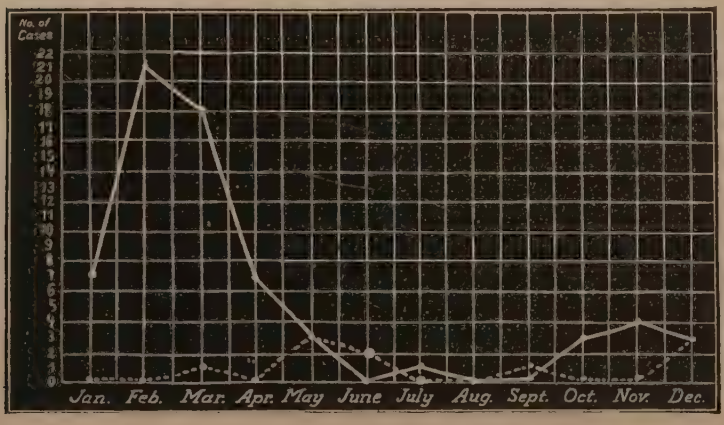
Two groups of cases occur, the first in sucklings (up to say the twentieth month of life) and known as tetania infantum, the second in the period from the third year of life on (tetania puerorum). The latter is symptomatically much like the tetany of adults.

In tetania infantum, carpopedal spasms occur; or they may be laryngospasm or general convulsions (eclampsia infantum). The diagnosis is most easily made by the demonstration of galvanic (and especially of anodic) hyperexcitability.

I. According to Age



——————— Intermittent Form; ..... Persistent Form



II. According to the Month of the Year

Fig. 13. Diagrams of 80 cases of tetany observed in the Children's Clinic at Graz during the years 1890 to 1897. (After T. Escherich.)

This tetany of sucklings does not seem to be limited geographically, as is epidemic tetany, nor is it restricted to certain seasons. That it is more prevalent during the "tetany months" in Graz is well shown in Fig 13. Tetany in children is not common in summer, when summer diarrheas are prevalent, and opportunity for autointoxication would seem to exist (Potpeschnigg).

Careful electrical studies of tetania infantum have been made in this country by H. B. Wilcox (1911), J. P. Sedgwick (1912) and J. B. Holmes (1916).

The Canadian school (Alan Brown, Almon Fletcher), more or less in accord with the Breslau school, have laid emphasis, as we have seen, upon the importance of superheated foods and of a high carbohydrate diet in the etiology of infantile tetany. They think that the diagnosis of the disease is suggested if renal inactivity appears in constipated infants that are fed on superheated foods of high carbohydrate content. Their studies of the mineral metabolism in infants suffering from tetany have also been referred to above.

Moll (1913) asserted that infantile tetany is due to intestinal intoxication, basing his view upon experiments made upon rabbits. He found that, on feeding young rabbits cow's milk, he produced, in addition to symptoms like prominent abdomen, rough coat, and retarded growth, an increase of the excitability of the motor nerves. The phenomena could be made to disappear by feeding green leaves and vegetables along with the milk diet. These studies of Moll suggest that there may be a vitamin element concerned in the origin of infantile tetany.

The effort has been made to discover the presence of histological changes in the parathyroid glands of children that have died from infantile tetany. Thus, Erdheim and Yanasse (1907) made the interesting observation that histological changes were not demonstrable in the parathyroid glands of children that during life had shown no increase of electrical excitability, whereas hemorrhages, or the remains of hemorrhages, could be demonstrated in the glands of those that had during life shown an increased excitability of the motor nerves. They assumed that these hemorrhages had occurred during the process of birth and that they had remained demonstrable for as long as twelve months after birth.

Though many internists and pediatrists lean to the view that tetany in sucklings is parathyrogenous in origin, there is still some doubt of this, even among the best informed. Heubner has suggested that, instead of the term "tetany," we apply the unprejudiced name "spasmophile diathesis" to the phenomena of hyperexcitability that are met with in children.

There seems but little doubt that in tetany regions, maternity tetany and the tetany of infections and intoxications are recruited from the group of so-called "cured cases" of childhood tetany.

The trophic disturbances (enamel defects in the teeth, nuclear and cortical cataracts) demonstrable in later life in persons who have suffered from tetany in childhood, have been referred to, at length, above.

8. The Experimental Production of Tetany in Human Beings by Means of Forced Respiration and the Occurrence of Tetany in Pathological Hyperpneas

An important paper has recently appeared, in which the proof has been brought that tetany can be experimentally produced in human beings by means of forced respiration. Grant and Goldman (1920), working in Professor Erlanger's Department of Physiology in Washington University, St. Louis, have brought this proof through a series of most carefully conducted experiments.

Having noticed, in persons subjected to a period of forced respiration, that the urine collected at the end of the period was cloudy, owing to alkalinity and the precipitation of phosphates, and surmising that the overventilation, through removal of CO_2 from the blood, had tended to make the blood more alkaline, and that, as a result of this, alkali had been excreted by the kidneys, in order that the hydrogen ion concentration in the body might be kept constant, these investigators undertook a further series of experiments to test the validity of their conjecture.

In some 23 experiments (exclusive of one control), the subject, lying on his back, breathed as deeply as possible, at the rate of about 14 times per minute (in time with a metronome). Symptoms of tetany developed in all the experiments within a short period (varying from 15 to 60 minutes), the diagnosis being based upon the presence of carpopedal spasms, Chvostek's sign, Trousseau's sign, Erb's phenomenon, and, in one instance, a tetanic convulsion.

The attention of Grant and Goldman was drawn to the occurrence of the tetany in their very first experiment. The subject, taking 15 deep breaths per minute, felt tingling in his fingers at the end of ten minutes. Five minutes later the muscles of his face felt stiff and he experienced some difficulty in articulation. In their second experiment (another subject) tingling of the tongue also developed, and at the end of 40 minutes, on inflating of the cuff for a blood pressure determination, the typical "obstetrical hand" of tetany was involuntarily assumed.

The two subjects, who appear to have been the two investigators themselves, were found on repeated experiments to differ somewhat in their reactions. In the one, spasticity of the facial muscles developed after breathing deeply for about ten minutes, when Chvostek's sign became easily elicitable. On continuation of the forced respiration, the spasticity in the facial domain increased until spontaneous contractions that puckered the lips and made articulation difficult occurred. Meanwhile, numbness and tingling had appeared in the hands, and a little later carpal spasms spontaneously set in. After cessation of the forced respiration, Chvostek's sign remained positive, a slight reaction being obtainable as long as twenty

minutes afterwards. In the other subject, though Chvostek's sign was less pronounced, the spasm of the hands was more marked. A little headache was noticeable early in the experiment. Tingling of the hands began in about 15 minutes, becoming more intense until marked spontaneous spasms of the hands occurred, Trousseau's sign becoming demonstrable several minutes before the onset of the spasms. In two of the experiments this subject exhibited spasm of the feet, but he did not in any of the experiments develop spontaneous spasm of the facial muscles. In one experiment he went into a complete tetanic convulsion (scream, general rigidity, opisthotonos, extended extremities). Both subjects experienced tingling in the muscles of the trunk on several occasions in experiments in which the forced breathing was prolonged. Erb's sign, tested for in two of the experiments, was positive; hyperexcitability (both cathodal and anodal) developed for both opening and closure contractions.

The following protocol of an experiment on the second subject gives a good idea of the sequence of events and of some of the metabolic findings:

SUBJECT A. G.

Time	Phenomena
Before deep breathing	Alveolar CO_2 tension 40 mm. Urine pH 4.9. Blood pH 7.4. Plasma CO_2 capacity 63.6 vol. per cent.
After deep breathing	
0 minute	Starts deep breathing, rate 12 per minute.
10th minute	Slight headache.
13th minute	Tingling in hands.
16th minute	Trousseau's sign obtained. Chvostek slightly positive.
17th minute	Both hands tingle markedly.
20th minute	Spasm of both hands.
21st minute	Alveolar CO_2 tension 20 mm.
22nd minute	Blood collected. pH 7.5. Plasma bicarbonate 45.8 vol. per cent.
23rd minute	Spasm of feet. No facial spasm. Deep respiration stopped.
25th minute	Urine collected. pH 7.9.

In each experiment the alveolar carbon dioxid tension was measured at the beginning and at the end, use being made of the Plesch bag method of collecting the air and of Marriott's colorimetric method for determining the CO_2 tension. The urine was analyzed for H-ion concentration (method of Henderson and Palmer), for titratable acidity to phenolphthalein as indicator, and for ammonia content (permutit method of Folin). In the blood, the H-ion concentration was determined (after dialysis;

colorimetric method of Levy, Rowntree and Marriott), the carbon dioxid capacity was measured (method of Van Slyke), and the calcium content was investigated (method of Lyman). In summary, it was found that, as a result of the fall of the alveolar CO_2 tension from overventilation, there is (1) a reduction in the H-ion concentration of the blood, (2) a reduction in the CO_2 capacity of the plasma, (3) a change in the reaction of the urine to the alkaline side, (4) a decreased output of ammonia in the urine, and (5) a slight increase in the calcium content of the blood serum. The graph of the experiment, of which the protocol was given above, is reproduced in Fig. 14. It shows the synchronous changes in the alveolar air, the blood, and the urine.

Interpreting their findings, Grant and Goldman believe that the forced respiration, by washing CO_2 out of the alveoli, reduces the CO_2 content of the blood, thus tending to make the blood more alkaline than normal. As a result, there is in the blood a disturbance of the $\frac{H_2CO_3}{NaHCO_3}$ ratio upon which the H-ion concentration depends. On the reëstablishment of this ratio, $NaHCO_3$ passes out of the blood plasma into the tissues, some of it being excreted by the kidneys. But the CO_2 is washed out of the blood more quickly by the overventilation than can be compensated for by reduction of the amount of the $NaHCO_3$ (by excretion or otherwise), and so the alkalinity of the blood is actually increased. The body tries to compensate for the increased alkalinity of the blood by reducing the amount of ammonia formed, and the lowered acidity of the urine depends partly upon increased excretion of alkali, but principally upon a retention of acid radicals.

These authors conclude, then, that, on overventilation, a true "alkalosis," in the sense of an actual change in the H-ion concentration, develops in the body; and the alkali reserve undergoes a reduction, owing to the elimination of the $NaHCO_3$ from the body fluids in the effort to maintain the H-ion concentration at a constant level. In "acidosis" there is also a reduction of alkali reserve, and, as Grant and Goldman point out, the coexistence of increased alkalinity of the blood with a reduction of alkali reserve reveals the inadequacy of the terms "alkalosis" and "acidosis."

On discussion of the etiological relationship of the alkalosis to the tetany produced, Grant and Goldman comment, first, upon the two prevailing views regarding the conditions of metabolism that can be responsible for tetany, (1) the view that tetany is due to calcium deficiency, and (2) the view that it depends upon a disturbance of the acid base equilibrium in the body. The calcium content of the blood was slightly increased in their experiments rather than reduced, but they suggest that this fact might be interpreted as due to a mechanism that tries to compensate for a loss of "active" calcium. The calcium was not, however, precipitated in the blood in their subjects, for the analysis was unaffected by centrifuging the serum.

They admit the possibility of the calcium being "precipitated" as extremely minute particles that are held in solution by the colloids of the serum, in which event it might not be removable by the centrifuge. In

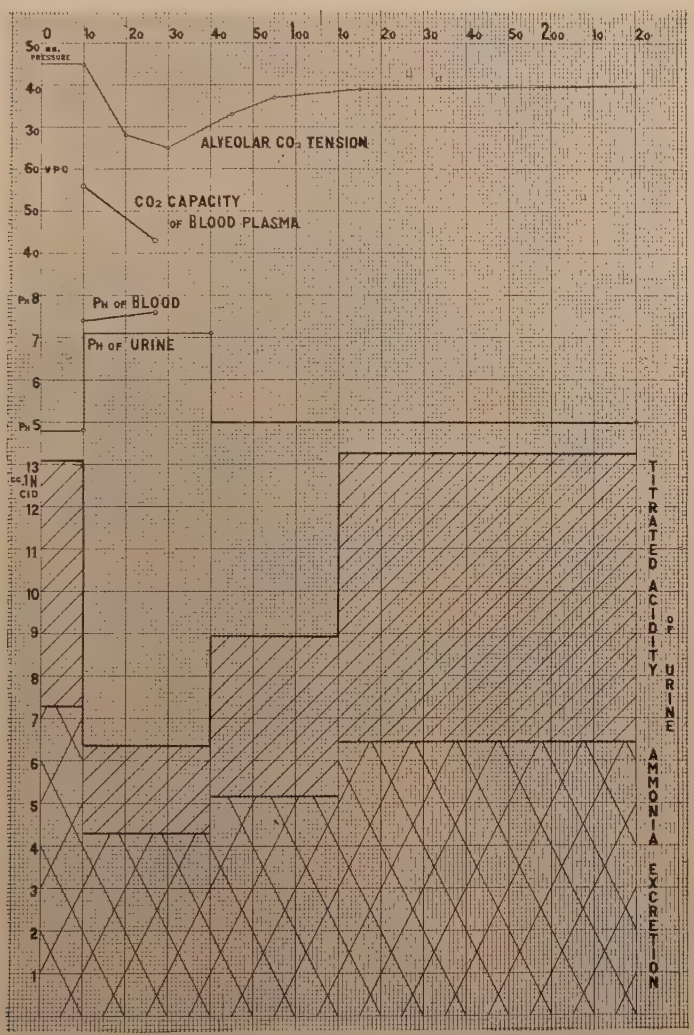


Fig. 14. Graph of experiment showing the synchronous changes in the alveolar air, the blood and the urine during the forced respiration leading to manifest tetany in a human subject. (After S. B. Grant and A. Goldman, Am. J. Physiol., Balt., 1920, lii, 209.)

their opinion, the alkalosis they observed probably caused the tetany by heightening the excitability of the nerves. Since tetany occurs under many circumstances, they think it improbable that it can be attributed in all cases to a single etiological factor; on the contrary, any condition that

heightens the irritability of the peripheral nerves may, they think, give rise to this interesting symptom complex.

On reviewing the bibliography of forced breathing, Grant and Goldman found a number of observations by other investigators of symptoms suggestive of tetany during the process. Thus, Vernon (1909) noticed, on the production of prolonged apnea in himself, tonic rigidity of the muscles of the hands and even temporary paralysis. Yandell Henderson (1909) made the same observation as Vernon during voluntary hyperpnea in several subjects, and even more frequently heard complaints of prickling sensations in the extremities, or in the face and the entire body; in one instance a "shivering fit," like that of a chill, involved all the muscles of the

Fig. 15. Attack of tetany in a patient suffering from Paroxysmal Hyperpnea during convalescence from epidemic encephalitis. (After L. F. Barker and T. P. Sprunt, 1921.)

body. And Hill and Flack (1910) reported "feelings of numbness in the limbs," a "spastic state of the hands," "twitching of the facial muscles," a sensation as though the mouth were "pursed up in the form of an O, so that speaking became difficult," and contractions of the lid closing muscles of the eyes, in subjects of voluntary hyperpnea. None of these investigators, however, identified these paresthetic and spastic phenomena with the symptoms of tetany!

It is just possible that the tetany observed by Stein (1916) in patients under slight anesthesia may have been due to overventilation.

It is interesting that two Canadian investigators (Collip and Backus) also observed the occurrence of tetany during forced respiration and that their paper was published in the *American Journal of Physiology* a few months before the paper by Grant and Goldman appeared.

Following upon these studies by the experimental physiologists, Barker

and Sprunt (1921) observed the occurrence of manifest tetany during paroxysmal hyperpnea in a neurotic patient convalescent from lethargic encephalitis, apparently the first observation of tetany due to a pathological (non-experimental) hyperpnea. (Fig. 15.) From now on it will be important to watch for manifest tetany and to test for latent signs of tetany in the various pathological hyperpneas that are met with clinically.

9. Unitary Conception of Tetany

As has been repeatedly hinted in the preceding pages, the conception of a unitary pathological-physiological basis, namely, a parathyroid genesis, for all forms of human and animal tetany has steadily grown in favor, until now it has become widely accepted, though still with reservations by the more conservative.

It was for the tetany following operations upon goiter that the foundation was laid, stone by stone, for the absolute proof of a parathyrogenetic origin. The building stones of this proof form an interesting series, as follows:—(1) the clinical observation of the occurrence of tetany after strumectomy; (2) the discovery of the parathyroid glands; (3) the demonstration that parathyroidectomy alone causes tetany, that thyroidectomy alone causes myxedema, and that thyroparathyroidectomy causes tetany plus myxedema; (4) the finding of parathyroid glands in the mass removed in strumectomy in cases in which outspoken tetany occurred; (5) the absence of tetany in complete thyroaplasia, if the parathyroids be normal; (6) the absence of tetany on removal of the middle portion of the thyroid gland in so-called "tongue goiter"; (7) the relatively frequent appearance of tetany on removal of the lateral lobes of the thyroid, while leaving the isthmus intact; (8) the relief of tetany by the administration of parathyroid substance; and (9) the cure of tetania strumipriva by means of transplantation of the parathyroid gland.

Through the edifice thus gradually erected the parathyroid origin of tetania strumipriva was made absolutely clear; but there has been some hesitation on the part of clinicians in accepting the doctrine that all the other forms of tetany are also of parathyroid origin, for in these other forms it is harder to prove that there has been an abolition or a diminution of the parathyroid functions. Opportunity for the pathological-histological examination of parathyroid glands in forms of tetany other than tetania strumipriva are not common. In the few cases in which the parathyroids have been examined post mortem, pathological-histological changes have sometimes been found, though not always; and those who assume a parathyroid origin for all forms of tetany have been compelled to fall back, in many cases at least, upon a functional defect of the parathyroid glands without demonstrable histological lesion. Comparative clinical studies,

however, of the different forms of tetany, and investigations along experimental physiological lines, have strongly indicated the pathogenetic significance of the parathyroid glands in every form of tetany. I think that the more conservative clinicians have, however, been right in holding their minds open, for it is not at all inconceivable that in the last analysis tetany may be due to some disturbance of intermediary metabolism that is caused often by parathyroid insufficiency but sometimes by conditions other than hypoparathyroidism.

Experimental removal of the thyroid and parathyroid glands simultaneously in animals gives rise in them to all the well known signs of tetany and, in addition, to spastic contractures, to intention spasm and sometimes to epileptiform convulsions. There is often in these animals, as in spontaneous tetany in human beings, marked fluctuation of the symptoms. The striking agreement between this tetania thyroparathyropriva of animals and the tetania strumipriva of human beings lends support to the view that the tetany in these experimental animals depends upon the loss of their parathyroid glands and has the same physiological basis as the tetany appearing in the tetania strumipriva of man.

When one examines comparatively the other forms of human tetany, including the idiopathic tetany of workmen, the tetany associated with gastrointestinal disturbances, the tetany in acute infectious diseases and in intoxications, the tetany of maternity, and the tetany of childhood, the remarkable agreement as regards the symptoms presented, despite the manifold conditions of their occurrence, is very striking. The galvanic and the mechanical excitability of the nerves is increased, the muscle spasms determine an obstetrical position of the hands, and, in addition, spasms of isolated muscles, of muscle groups, or of the musculature as a whole, are common to them all. Moreover, in all of them too, as Pineles has emphasized, spastic contractures, flaccid pareses, myotonic symptoms, epileptiform atttacks, and rapid changes of the individual symptoms, are a common feature. Instances of the latter group of symptoms may only occasionally be met with among members of a group, but they are not with the same regularity met with in simulating pathological conditions like tetanus, genuine epilepsy, or the eclampsia of pregnancy. The same may be said of the trophic disturbances that involve the ectodermal structures (hair, nails, teeth, crystalline lens), for they are all met with in the several different forms of tetany, a fact that is very well illustrated in the accompanying table (see next page) translated from an article by Pineles.

Examination of this table will quickly convince any one of the striking agreement that exists between human tetania strumipriva on the one hand, and the other forms of tetany in human beings, including the so-called idiopathic, on the other. The agreement is closest, perhaps, between tetania strumipriva and tetany of workmen, doubtless because these two forms have been better studied and occur more frequently than the other forms.

	Galvanic Excitability	Mechanical Excitability	Chronic Spasms	Flaccid Pareses	Myxœdematous Phenomena	Epileptiform Attacks	Obstetrical Hand	Falling out of Hair and Nails	Cataract	Gastro-intestinal Disturbances	Prevalence During March and April
Tetany in animals after removal of both thyroid and parathyroid glands.	Markedly increased	Slightly increased	Sometimes present	Sometimes present	Sometimes present	Sometimes present		?	?		
Tetania strumipriva in man.	"	Markedly increased	"	"	"	"	Marked	Present	Present		
Idiopathic tetany of workmen.	"	"	"	"	"	"	"	"	"	Present	+
Maternity tetany.	"	"	"	"	?	"	"	"	"	?	+
Tetany in association with gastro-intestinal diseases.	"	"	"	"	Sometimes present	"	"	"	"	Present	+
Tetany in children.	"	"	"	"	?	"	"	"	"	"	+
Tetany in infectious diseases.	"	"	?	?	?	?	"	?	?	" (Typhoid cholera.)	?

Since the definite proof has been brought that the loss of function of the parathyroid glands accounts for the origin of tetania strumipriva, there has seemed to many good reason to believe that the other forms of tetany also are due to loss, or to diminution, of the functions of the parathyroid glands. When the parathyroid glands are not properly functioning, some poison, they think, gets an opportunity to act upon and to injure the nervous system, so that the symptoms of tetany appear. Just how the parathyroid glands become insufficient, and just how the "tetany poison" gets the opportunity to work in forms of tetany other than tetania strumipriva, are problems that remain still, they admit, to be worked out. In other words, though the general pathogenesis that they assume for tetany would seem to have reached a satisfactory stage in the establishment of the doctrine of parathyroid insufficiency as the pathological-physiological basis, it is admitted by them that there is still room for extensive clinical and experimental study before the precise etiology of the disease in its several forms can become clearly understood. But to the more conservative, this view, though interesting, need not seem final. The experimental production of tetany in man by forced respiration (*vide supra*) would make it seem possible that any condition that heightens the excitability of the nerves in a certain way may be responsible for the occurrence of tetany. In the last analysis, may not this heightening of excitability depend upon the withdrawal of calcium from the neurons, owing to either acidosis or alkalosis, the latter conditions being producible by a variety of causes, of which parathyroid insufficiency is one and hyperpnea another?

10. The Poisonous Substance in Tetany

The phenomena of tetania strumipriva in man and the symptoms that follow complete extirpation of the thyroid and the parathyroids in animals have impressed many investigators as those of an acute intoxication of some sort. The idea quickly arose that the symptoms might be due to some form of auto-intoxication, dependent upon the removal of a "detoxicating" organ. Some investigators assumed that the detoxicating organ is the parathyroid, and that the intoxicating organ is the thyroid. But out of accord with this view were the observations that a certain vicarious rather than an antagonistic relationship appears, as we have already seen, to exist between the thyroid and the parathyroids. The symptoms on complete removal of both thyroid and parathyroids simultaneously are less marked, according to Vassale and Generali, than those following parathyroidectomy alone, and these authors assumed that the explanation lies in the removal (in thyroparathyroidectomy) of the poison producing organ (the thyroid) along with the detoxicating organ (the parathyroids). It has been asserted by Van Calcar, also, that when the thyroid is not removed at parathyroid-

ectomy the tetany is more violent than when it is also removed, and, further, that subsequent removal of the thyroid lessens the violence of the tetany. Still, as Biedl has pointed out, the disease picture of postoperative tetany, as regards intensity of symptoms, course and duration, is so extremely variable that it would be dangerous, from a consideration of their behavior alone, to draw direct conclusions regarding the kind of functional connection that exists between the thyroid gland and the parathyroids. Moreover, numerous experiments made by Biedl himself, and others made by Wiener, have failed to confirm the observations of a more violent tetany after thyroparathyroidectomy than after a pure parathyroidectomy. And many good clinical observers assert that the administration of thyroid substance exerts a definitely ameliorative effect upon the symptoms of tetania strumipriva. There does not seem, therefore, to be sufficient support for the detoxication hypothesis, at least in its original form, in which the thyroid was looked upon as the poison-making organ.

Accordingly, investigators at present assume in general a toxic substance arising somewhere in the organism, and speak of it as the "tetany poison of unknown origin." Uhlenhuth's studies point to its origin in the thymus gland.

Some evidence has been brought forward to show that the tetany poison is present in the circulating blood (MacCallum and Voegtlin, Fano and Zanda, Baldi, Biedl), for severe attacks of tetany can be quickly ameliorated by copious bleeding, the improvement lasting for twenty-four hours if some fresh normal blood be transfused after the venesection.

The attempts of Wiener to prove that the tetany poison, whatever it is, possesses the character of an antigen, to which the normal organism builds an antitoxin (self-immunization), seems improbable and certainly lacks sufficient experimental support.

When discussing the metabolism of tetany, we pointed to the multiple observations of an increased ammonia output in tetany. On account of this finding, the theory of ammonia poisoning and of carbaminic acid poisoning as an explanation of the intoxication in tetany was early put forward. Frouin (1910) asserted that he could produce typical tetany within twenty-four or forty-eight hours after removal of the thyroid apparatus by injection of three or four grams of carbaminate of soda, though when the injection of this substance was combined with that of a soluble calcium salt no signs of tetany appeared. But the theory that tetany might be due to disturbance of liver function with loss of power to destroy ammonia or diminution of that power, also developed by Carlson and Jacobson in 1910, has been given up, these latter authors themselves having shown in a later publication that there are essential differences between the muscle spasms due to tetany and those due to ammonia poisoning.

Since an increased ammonia output in the urine is usually a sign of

acidosis, it is not surprising that Morel, finding that the severity and duration of the signs of tetany correspond to the degree of acidosis existing, should have emphasized the importance of acid poisoning in the etiology of the symptoms. By the administration of betaoxybutyric acid, he asserted that he could shorten the lives of animals suffering from tetany following parathyroidectomy by at least two days, and he found further that he could prolong their lives, if he diminished the acidosis by administering sodium bicarbonate.

On the other hand, alkalosis rather than acidosis seems sometimes to exist in tetany. Wilson, Stearns and Thurlow (1915), and Wilson, Stearns and Janney (1915) observed a period of alkalosis in parathyroidectomized dogs just before an attack of tetany, though this alkalosis was neutralized by acid substances produced during the attack. Injections of acid and also of calcium salts relieved the tetany. They suggested that the calcium salts may have acted, in part at least, by causing a relative increase in acid radicals (formation of $Ca_3(PO_4)_2$ from the carbonates, thus liberating HCl).

The experiments of McCann (1918) also point to alkalosis rather than to acidosis as a cause of tetany, this alkalosis being due, perhaps, to a disproportion between the rates of secretion of acids and alkalies by the gastrointestinal tract. He found a marked increase in the CO_2 combining power of the plasma of the blood, coincident with the development of tetany after parathyroidectomy, and also following gastric operations that prevented the entrance of acid into the duodenum. He suggested that tetany following pyloric obstruction may be explicable by an alkalosis similarly conditioned.

In 1920, MacCallum and his collaborators observed that, when pyloric occlusion was experimentally produced in dogs and distilled water only was injected into the duodenum, the stomach continued to secrete HCl, the alkalinity of the blood increased, and symptoms like those of tetany appeared, though they could be prevented by injecting a solution of sodium chloride into the duodenum, or, after the symptoms had developed, they could be made to disappear by injection of the same substance into the blood. The calcium content of the blood plasma was not changed. They suggested that the tetany-like symptoms in these dogs might be due to a disturbance of the acid base equilibrium.

Even a temporary alkalosis produced by the therapeutic administration of alkalies may, apparently, call forth tetany. Thus, Howland and Marriott (1918) mentioned three cases of tetany in children following administration of sodium bicarbonate; in all three the calcium content of the serum was diminished. Harrop (1919) saw tetany appear in an adult after injection of sixty grams of $NaHCO_3$ intravenously. Binger (1917), by intravenous injection of sodium phosphate, had produced tetany in dogs and decrease of the calcium content of the serum, though, if the solution

injected had a H-ion concentration greater than pH_6, tetany did not occur, even though the content of the serum in calcium was decreased.

The loss of calcium observed during tetany attacks and the discovery that the administration of calcium will ameliorate the symptoms of tetany (MacCallum and Voegtlin, Netter) led many to think that the parathyroid glands exert a direct and specific influence upon calcium metabolism. The tendency at the present time, however, is to look upon the withdrawal of calcium as due to an acidosis, intercalated between it and the hypoparathyroidism, the body, in its attempts to neutralize the acidosis, catching up ammonia in intermediate metabolism and also, for the same purpose, gradually exhausting the stores of the tissue cells in such kations as calcium and magnesium. The marked disturbance in the kation balance in the body thus brought about favors the occurrence of muscular spasms, as we know from the important researches of Sabbatini, Jacques Loeb, J. B. MacCallum and S. T. Meltzer (*vide supra*).

In the search for the tetany poison, another road has been taken by those who look for it in some derivative of the degradation products of the proteins on the one hand, or of the nucleic acids and mononucleotids on the other. Thus the resemblance of the phenomena of tetany to those of chronic ergotism (Fuchs (*a*)) led Biedl to compare the toxic substances in ergot (and the effects they produce) with the hypothetical tetany poison (and the clinical phenomena of tetany). The active principle in ergot seems to be beta-imidazolylethylamin (Barger and Dale), an amino base that is formed when histidin undergoes putrefaction (Ackermann). It seemed possible, therefore, that the tetany poison might consist of amino bases and especially of the base known as beta-imidazolylethylamin. Biedl found that repeated subcutaneous injections of this substance into cats caused an increased excitability of the peripheral nerve trunks, fibrillary twitchings in single muscles, and the peculiar shaking of the paws typical of tetany in cats. Histidin, it will be recalled, is an amino acid of the aromatic series and, in particular, one of the amino acids of the heterocyclic series.

The question next arose whether derivatives of amino acids of the fatty acid series could be responsible for the origin of a tetany poison. Thus, attention has been directed recently to the guanidino acids that belong to the amino acids of the fatty acid series. The best known member of this group is arginin, which is alpha-amino-delta-guanidino-valerianic acid, whereas histidin is beta-imidazo-alpha-amino-propionic acid. In 1913 and 1916 W. B. Koch (*a*) (*b*) (*c*) took up the study of experimental tetany in dogs. In the urine of these dogs he found two guanidin substances, one was methyl cyamidin, the other trimethylamin. These substances, when injected into rabbits, produced typical tetany. Koch came to the conclusion that somewhere in the body methyl cyanimid is generated. He believes that this substance has a physiological effect in normal animals, but that, after parathyroid extirpation, it accumulates in toxic quantities and is respon-

sible for tetany and for death. He asserts that all salts that act as diuretics aid in the excretion of the tetany toxin and that the especially beneficial effect of calcium is due to the additional influence of its sedative or depressing effect upon nervous excitability. According to Koch's theory, tetany is simply an intoxication; the toxin is subdued by diuresis or by neutralization, and it cannot exert its effects in the presence of the normal secretion of the parathyroid glands.

These studies of Koch assume an especial interest in the light of the investigations of Paton and Findlay (*c*). In researches directed toward the etiology of tetania parathyropriva and its relationship to guanidin and methylguanidin intoxication, these authors, after concluding that there is no direct interrelationship between the parathyroids and the thyroid, assert, (1) that there is no evidence that the parathyroids exercise a direct controlling influence on the central nervous system, (2) that the symptoms of tetania parathyropriva are not primarily due to any decrease in any constituent of the body such as calcium ions nor are they due to any increase in ammonia, xanthin or beta-imid-azolyl-ethylamin, but (3) the symptoms of tetany are identical with those producible by the administration of salts of guanidin and methylguanidin. These assertions are supported by the findings of several of Paton's coworkers. Burns and Sharpe found a marked increase in the amount of guanidin and methylguanidin in the blood of dogs after parathyroidectomy and in the urine of children suffering from idiopathic tetany. G. M. Wishart observed that the serum of parathyroidectomized dogs acts upon the muscles of the frog in the same way as do dilute solutions of guanidin and methylguanidin. D. A. Burns found that the administration of guanidin hydrochlorid to dogs caused similar metabolic phenomena to those observable after parathyroidectomy in dogs, and concludes that the two states are probably identical. Paton and Findlay, summarizing the results of the investigations, concluded (1) that the parathyroids regulate the metabolism of guanidin in the body and by so doing probably exercise a controlling influence on the tone of the muscles, and (2) that, since tetania parathyropriva and idiopathic tetany are identical as regards their character and metabolism, the parathyroids are, in all probability, implicated in the latter as well as in the former, despite the fact that the histological evidence therefor is not yet conclusive.

As to the part that ferments play in the production of the tetany poison, but little is as yet known. When discussing the metabolism of tetany (*vide supra*) I have expressed the conviction that parathyroid insufficiency may mean a ferment insufficiency and experiments in this direction should certainly be undertaken.

The vagueness and obscurity of these various conceptions of the etiology and pathogenesis of tetany prove that, as yet, our knowledge of the subject is too immature to permit of a clear portrayal. The facts and ideas that have been brought forward are like a pack of scattered cards.

They represent mere gropings toward the satisfactory explanation that subsequent research will render possible.

11. The Site and Mode of Action of the Tetany Poison

An examination of the symptoms and signs of tetany has shown us very clearly that, both in man and in experimental animals, the nervous system is profoundly affected, chiefly in the direction of increased excitability of the motor, sensory and visceral nerves to mechanical, chemical and electrical stimuli.

All the principal signs of tetany—carpopedal spasms, Erb's phenomenon, Trousseau's sign, Chvostek's phenomenon, Hoffmann's phenomenon, increased epinephrin sensitiveness, increased pilocarpin sensitiveness, epileptiform attacks—point to increased excitability. Signs of depression of excitability, at least in certain domains, are, however, also met with, including diminution of the deep reflexes, flaccid pareses, diminution in the efficiency of the gastric and intestinal motor mechanisms (Carlson), and increased heat loss due to depression or to paralysis of the vasoconstrictor mechanism of the blood vessels (Smith).

In view of the obvious alterations in the nervous functions in tetany, many attempts have been made to determine the exact localization of the action of the poison in the nervous tissues. The papers of O. Lanz (1894), W. G. MacCallum (1909), Carlson and Jacobson, F. T. Shepherd and Wesley Mills, Falta and Rüdinger (1909), H. J. Mustard (1911-12), and A. Biedl (1913) bear upon this phase of the subject.

In summary, it may be said that the observations thus far made, though they permit us to state that there is a heightened excitability of the nerve centers and of the peripheral nerves, and that certain central (probably subcortical) neurons are affected, do not adequately reveal the exact anatomical and histological localization of the specific effects of the tetany poison. It is conceivable that some of the mechanisms that participate in the production of the remarkable tonic contractures that characterize the so-called decerebrate rigidity of experimental animals may be specifically acted upon by the tetany poison. Certain it is that the effect is exerted upon the neural mechanisms themselves and not directly upon the muscles innervated by the motor nerves. Furthermore, the change produced in the nervous system is not inflammatory in character, nor can it be merely a circulatory disturbance; it is probably of a toxic degenerative nature.

V. Pathological Anatomy and Histology of Tetany

The pathological changes that have been observed in the parathyroid glands in tetany and in other conditions are fully described in the article by Oscar Klotz in this system (*q.v.*). Hemorrhages, scars, cysts, atrophies,

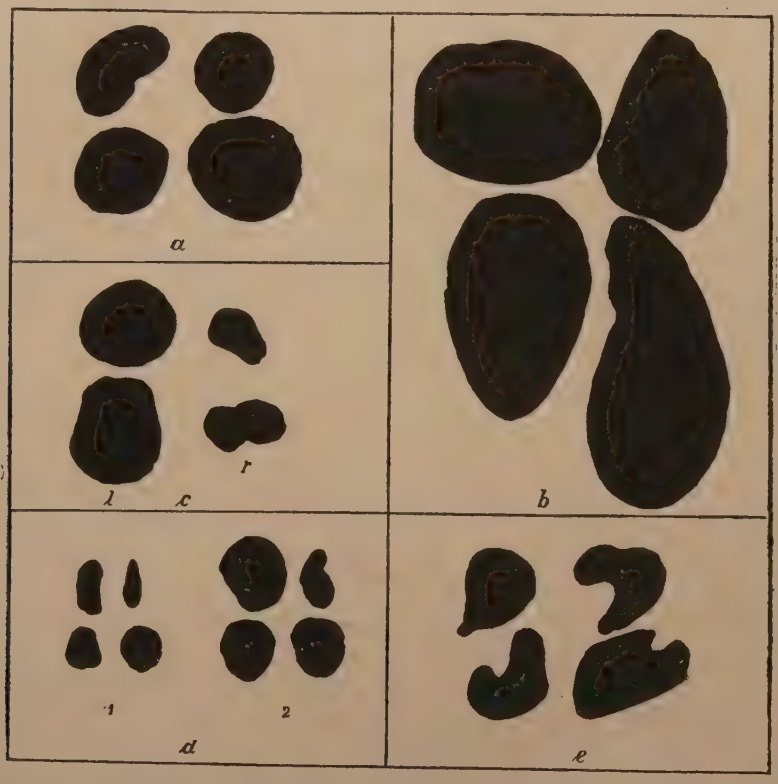


Fig. 16. The shadow pictures represent the greatest cross section of the parathyroid gland magnified about eight times. (a) Average size of normal parathyroid gland of children (up to one year). (b) Average size of normal parathyroid gland of adults. (c) Parathyroid gland from a five months old child; the left parathyroids are of normal size, the right are definitely smaller (as a result of hemorrhages). (d) Hypoplastic parathyroid glands from children with lues hereditaria (four and six weeks old). (e) Hypoplastic parathyroid gland of a twenty-five years old adult with tetany. (Compare with (b).) (After W. Haberfeld, Virchow's Archiv, 1911.)

round celled infiltration, and ruptured lymph spaces are the findings that have most often been met with. In Europe, Haberfeld (1910-11) has published important articles on the size (Fig. 16) and the histology of the parathyroid glands in tetany. B. S. Oppenheimer (1911), and Pröscher and Diller have, in the United States, made reports upon the pathological histology of the parathyroid glands in tetany. It must be remembered,

however, that similar findings have been made in the parathyroid glands of persons who during life have shown no signs of tetany.

The pathological histology of the nervous system of animals suffering from experimental tetany has been carefully studied by W. G. MacCallum, who found signs of acute degeneration, with swelling of the nuclei of the anterior horn cells of the spinal cord, as well as changes in the Nissl bodies (chromatolysis) of the cells of the cerebral cortex.

In a case of tetany complicating acute miliary tuberculosis, M. Winternitz demonstrated the presence of miliary tubercles within the parathyroid glands themselves.

VI. Course of Tetany and Its Termination Prognosis

The course and termination of tetany and the sequelæ vary somewhat, according to the form of the disease and the age when the tetany occurs.

1. Prognosis in the Tetany of Childhood

Three sets of statistics are available, those of Potpeschnigg, those of Phleps, and those of von Frankl-Hochwart.

Potpeschnigg's statistics include 119 cases. Of these, no less than 23 per cent died during their first admission to the hospital and on tracing, those that did not die on their first admission, it was found that 19 patients had died in subsequent attacks. Some 24 of the children were found still living and were reëxamined; of these, five showed no signs of tetany; four suffered from chronic tetany, and the other fifteen exhibited severe nervous or general disturbances (mental deficiency, infantilism, etc.).

Phleps reviewed the histories of 103 patients, 39 of whom certainly had tetany within the first two years of life, and 14 more probably had it during that period. An analysis of these 53 cases showed that only five were, in later life, entirely free from symptoms. An analysis of these 103 cases, whose average age was 25 years at the time of the analysis, revealed the presence of cataract in 66 of them, epilepsy in 17, and enamel defects of the teeth in 53.

Von Frankl-Hochwart could secure full reports of only 55 of his 160 cases. Of these, eleven had died in early life, seven still suffered from tetany, nineteen had symptoms that he designated as "tetanoid," that is to say, they manifested one or more of the latent signs of tetany, six, though still quite young, were chronic invalids, manifesting a condition that resembled myxedema, and only twelve were healthy. Thus, no less than four-fifths of the 55 were dead or were permanently invalided.

Obviously, therefore, childhood tetany has a high mortality at the time of its occurrence (over 20 per cent), and the children that recover from the first attack run the risk of dying later on from a recurrence of the tetany, or of becoming permanently handicapped by chronic illnesses of various sorts, including epilepsy and cataract.

2. Prognosis in Tetany after Strumectomy

If the postoperative tetany be violent and especially if it set in at once after the operation, death almost always occurs within a few days, though occasionally a patient will live for a few weeks and then succumb.

In only a few cases in which outspoken tetany develops immediately after the operation do the patients recover completely.

In still another group, the patients do not die from the tetany, which may indeed entirely disappear, but they develop myxedema, and have to take thyroid extract continuously.

Since the operation for goiter has been greatly improved, so that the parathyroids are left in and are only rarely injured at the operation, tetany has become rare after strumectomy; it is only exceptionally, as in extensive carcinomatous growth, that the parathyroids must be sacrificed by the surgeon. In certain other very difficult goiter operations, too, the parathyroid glands may undergo injury. A temporary parathyroid insufficiency still occasionally occurs after simple goiter operations, doubtless owing to slight inadvertent injury to the parathyroid glands either directly, or through interference with their blood supply. In these cases it is, as a rule, easy to tide the patient over by suitable treatment to a time when the parathyroids have regained their full function (see Therapy). Even though recovery occur from postoperative tetany, it must be borne in mind that there may result a permanent hypoparathyroidism, in which event a pregnancy, an infection, an intoxication, or a gastro-intestinal disturbance, later on in life, may call forth again the symptoms of tetany. Some patients go through the first pregnancy after operation without difficulty, but develop tetany during the second pregnancy, during a puerperal period, or during prolonged lactation. Successful transplantation of one or more parathyroid glands in tetania strumipriva makes the prognosis good.

3. Prognosis in Idiopathic (Epidemic-Endemic) Tetany and in Tetany in Infections and Intoxications

These are the cases in which the prognosis is by far the most favorable. No death, so far as I know, has been recorded due directly to the so-called idiopathic tetany of workmen. If the patients leave their homes and enter

the hospital, the symptoms often pass off very quickly, say within a few days. Patients who stay at home and even some of those who are treated in a hospital, may have attacks for several weeks. The attacks, however, gradually grow milder and, later, they disappear entirely, though it may be several weeks or even several months before the patients are quite well, that is to say, before latent signs of tetany (Trousseau phenomenon, Erb phenomenon, etc.) disappear. It should not be forgotten, however, that those who are apparently cured are very liable to relapses in succeeding years during the tetany months. In Vienna it is not uncommon to have patients return year after year, in March or April, with an attack of tetany. It is said that, after a time, the patients grow so accustomed to these seasonal attacks that they no longer report to the hospitals for treatment. Among the patients who suffer from recurrent attacks, trophic disturbances frequently develop.

4. Prognosis in Tetany Associated with Gastrointestinal Diseases

Under medical treatment alone, gastric tetany has been found to be a very serious disease. Thus Bouveret and Dĕvic, 1892, reported the mortality as 40 per cent and the statistics of other investigators indicate that the disease when treated medically is even more grave than this. Loeb in 1890 reported a mortality of 71.4 per cent, Heim in 1893 a death-rate of 76 per cent, and Albu asserts as high a mortality even as 77.5 per cent in tetania gastrica, treated medically. In other words, approximately 70 per cent of the patients die, and only 30 per cent recover under non-surgical measures.

On the other hand, if cases of tetania gastrica be treated surgically, the figures are reversed. According to Wirth, of 21 cases operated upon, 17 were permanently cured, one was improved, and only three died; in other words, under surgical therapy, 85 per cent were cured and only 15 per cent died. Doubtless, as knowledge of the favorable effects of surgery in this special group of cases becomes more widespread, the patients will be operated upon earlier and still better statistics can later on be reported.

5. Prognosis in Maternity Tetany

The tetany of pregnancy or of the puerperium is sometimes fatal. Trousseau, as early as 1848, described a fatal case. The woman had had syphilis and had been delivered of a dead child, but before delivery she had become much emaciated and had suffered from severe diarrhea. At first she improved a little, but about two weeks after delivery her feet began to swell and she complained of weakness in the legs. During one

night she had a violent headache, and the next day an extraordinarily severe attack of tetany, which involved the respiratory muscles, set in. The face of the patient became cyanotic, the breathing stertorous, the pulse accelerated and, after a short time, she died.

Tetany not infrequently develops during lactation, and this form, too, may be fatal.

During childbirth the tetany spasms may come on coincidently with the uterine contractions (Neumann), and it has been suggested that the stimulation, here starting in the uterus, is analogous to pressure on the nerve in the Trousseau phenomenon.

If maternity tetany has once occurred and the patient has survived, it is doubtful whether or not she should again be permitted to become pregnant. Should pregnancy inadvertently occur, it would be wise and legitimate to interrupt it, as tetany is likely to become more severe with each succeeding pregnancy.

In lactating women predisposed to tetany, it seems probable that the suckling of the child may act as a stimulus that will call forth a tetany attack (Völker). It has therefore been suggested that women subject to tetany who give birth to children should not try to suckle them themselves, but should employ a wet-nurse, especially as statistics show that tetany is very rare during lactation in women who do not suckle their children.

VII. General Diagnosis of Tetany

Typical tetany presents no diagnostic difficulty. The intermittent attacks of tonic contractions with characteristic distribution of the spasms in definite muscular domains, giving the well known attitudes (obstetrical hand, extended knee with supinated foot, carpopedal spasms), and their association with marked increase of the mechanical and of the electrical excitability of the motor nerves (with low values for the cathodal closure contraction) are marks that scarcely admit of confusion with any other clinical syndrome.

But every clinician of experience has been confronted with less typical cases of tetany in which the diagnosis was not easy. When the spasms are atypical, or when the tetany is latent and no spontaneous attacks occur, or when tetany is combined with other diseases, or when other diseases are present that simulate tetany though tetany is absent, mistakes may easily be made. In such cases, the examiner needs to be equipped not only with a thorough familiarity with the relative value for diagnosis of the several tetany phenomena, but also with a wide knowledge of general medicine, neurology and endocrinology, for the differential diagnosis, in obscure cases, depends often upon the summation of a whole series of minute details.

The *tonic spasms* are a constant symptom in the acute stages of tetany, but the form of the spasms may not be typical. Many variations (in attitude, duration, and severity) from normal type are met with. Thus, instead of the typical obstetrical hand with flexion of the elbow, the elbow may be extended, and the fingers may form a fist or a claw, or may be spread apart instead of being strongly adducted. Again, in the lower extremities, instead of the typical extension at the knee, there may be flexion; and instead of plantar flexion and supination of the foot, there may be dorsal flexion at the ankle. The duration of the spasms is, in turn, also exceedingly variable. And as to severity, instead of the typical violent attack, the spasms may be so mild that the patients do not mention them, but recall them only when asked specifically about them; in such instances, the patients complain rather of the paresthesias and the pain than of the spasms. In many patients the attacks of spasm appear only under the influence of some releasing factor (muscular overexertion, psychic trauma, infection, intoxication, pregnancy, menstruation, dilatation and curetting of the uterus, injection of tuberculin, acidosis, alkalosis, etc.).

One of the most constant phenomena in tetany, whether manifest or latent, is a positive finding on testing for increased mechanical excitability of the nerves, especially *Chvostek's sign,* or the *facial phenomenon* following a tap in front of the ear or below the zygoma. Though this sign may be positive in conditions other than tetany, noticeably in tuberculosis, epilepsy, hysteria, and pellagra, still, when it is present in a marked degree, it is one of the most important clews for diagnosis and should lead one to the making of a series of careful tests, the results of which will be decisive. Chvostek has asserted that the facial phenomenon is the "finest reagent we possess for detecting the existence of a functional disturbance of the parathyroid glands." It is exceedingly rare that, in tetany, the facial phenomenon is absent on repeated testing. It is the most constant and often the only symptom demonstrable in the latent periods of tetany. If a light tap, or stroking with the finger tip, over the trunk of the facial nerve calls forth contractions in the whole of the same side of the face, one can be sure that tetany exists. Even with Chvostek II, a positive finding is rare in any condition other than tetany. On a Chvostek sign of the third grade (Chvostek III) too much stress should not be laid, though it may excite in the mind of the examiner the suspicion that a slight functional disturbance of the parathyroid glands may exist.

Next to the increased mechanical excitability of the nerves the most important single test for tetany is the examination for increased electrical excitability of the motor nerves (*Erb's phenomenon*). When, on testing with the galvanic current, there is early response to anodal opening contraction and to cathodal opening contraction, and especially when anodal opening tetanus and cathodal opening tetanus are easily demonstrable, we

can be sure that tetany exists. Especially in the tetany of infancy is the test for increased galvanic excitability very important, as has been shown by the exact studies of Thiemich and of von Pirquet (*a*) (*b*) in Europe and by those of H. B. Wilcox, J. P. Sedgwick, J. B. Holmes, and others in America. Indeed, increased electrical excitability is now regarded as the most reliable sign for the detection of tetany in young infants. Marked alterations of the electrical excitability, such as we find in tetany, are not observable in any other disease, and if found to be present, they are like an outspoken facial phenomenon, decisive for the positive diagnosis of tetany. In latent tetany, and in the intervals between attacks in acute tetany, Erb's phenomenon is, however, less often found positive than is Chvostek's sign. A disadvantage, too, of the electrical excitability test is its circumstantiality. The electric battery must be at hand, and one must have some skill in applying it, though this skill is very easily acquired. The test for Chvostek's phenomenon, on the other hand, is so simple that it can be applied in a moment anywhere and by any one.

Trousseau's phenomenon is very helpful in the diagnosis of tetany, for when it is positive it is exceedingly characteristic, but it is not infrequently negative in undoubted cases of tetany, and may not be demonstrable even in cases of acute tetany. Moreover, when the tetany begins to die down, Trousseau's phenomenon tends to disappear more quickly than either Chvostek's sign or Erb's phenomenon. In hysteria, a so-called pseudo-Trousseau phenomenon is said sometimes to occur on pressure over the ovaries or upon a spinous process of a vertebra.

The test for the *leg phenomenon* of Pool, as well as that for his *arm phenomenon,* is easy to apply. According to Schlesinger, the test for the leg phenomenon will yield a positive result in some cases in which the test for Trousseau's sign is negative.

The *other tetany symptoms* (Hoffmann phenomenon, galvanic hyperesthesia of the acusticus, myotonic phenomena, fibrillation of single muscles, the tetany face, and trophic disturbances in the nails, hair, teeth and crystalline lens) should all be kept in mind and should be looked for in doubtful cases. In such instances, too, an injection of old tuberculin may call forth an attack and this test has therefore sometimes been applied for diagnostic purposes (Chvostek).

The positive signs and symptoms in tetany are found to vary greatly, presumably, according to the degree of insufficiency of the parathyroid gland that exists in different cases. According to degree of intensity of the tetany, the cases may be grouped as follows:—

1. *Mildest cases.* No symptoms of tetany present except a positive Chvostek's sign.

2. *Tetanoid state* of von Frankl-Hochwart. Paresthesias, feelings of stiffness in the muscles, with atypical cramps in certain circumstances (extension of the trunk on grasping objects, cramps in the calves on exten-

sion of the foot), a positive Chvostek's sign, often a positive Erb phenomenon, but very rarely a positive Trousseau phenomenon.

3. *Formes frustes* of von Frankl-Hochwart. No spontaneous typical muscle spasms, but Trousseau phenomenon positive, leg phenomenon positive, Chvostek's phenomenon positive, and Erb's phenomenon positive.

4. *Chronic tetany with mild recurrent attacks.* All signs of tetany present.

5. *Acute attacks of tetany.* The most outspoken symptoms of tetany are present.

These variations in the clinical picture of tetany doubtless depend, according to Chvostek, partly upon the degree of functional disturbance of the parathyroid glands that exists, partly upon variations in the power of the organism to adapt itself to the altered functions of these structures, and partly upon the existence and intensity of releasing factors. Or, it may turn out to be true that tetany of variable severity may occur, owing to metabolic vices that are independent of parathyropathies.

VIII. Differential Diagnosis of Tetany

Those modifications of the clinical picture in tetany that are often responsible for confusion with other diseases, nervous or infectious, will next be discussed. The conditions can be classified under three main headings, each with several subheadings:—

1. Conditions (other than tetany) in which hyperkinetic phenomena resembling those of tetany may occur. (a) Conditions in which tonic spasms involving the musculature as a whole may occur (tetanus, hydrophobia, strychnin poisoning, katatonia). (b) Conditions in which tonic spasms that involve local muscular domains occur (crampi musculorum). (c) Myoclonias and fibrillary twitchings. (d) Tics and habit spasms. (e) Conditions in which general convulsive states or fits occur (hysteria, psychasthenia, epilepsy, symptomatic fits).

2. Conditions (other than tetany) that may simulate the motor pareses sometimes seen in tetany (poliomyelitis, progressive central muscular atrophy, peripheral neuritis, progressive muscular dystrophy, myasthenia gravis, and encephalitis and encephalomyelitis).

3. Conditions (other than tetany) that may be associated with sensory phenomena resembling those of tetany (acroparesthesias, arthritides, Raynaud's disease).

1. Conditions (Other than Tetany) in which Hyperkinetic Phenomena Resembling Those of Tetany May Occur

a. Tonic Spasms Involving the Musculature as a Whole

Tetanus.—When, in tetanus, the cramps involve the muscles of the face, neck, jaws, and trunk, as well as those of the extremities, a syndrome similar to tetany may result. But the absence of the typical tetany signs (Chvostek's phenomenon, Erb's phenomenon) and a decrease of reflex excitability rather than an increase, usually permit one quickly to distinguish tetanus from tetany. The anamnesis also helps to differentiate.

Hydrophobia.—In hydrophobia the tonic spasm affects especially the muscles of deglutition (so-called "cephalic tetanus"). These muscles may, though rarely, be affected in tetany, but then the other tetany signs are present and there is no history of dogbite.

Strychnin Poisoning.—The paroxysms of muscle spasm in strychnin poisoning begin with clonic contractions that quickly become tonic, and between the single paroxysms there is complete muscular relaxation. Trousseau's phenomenon is absent. The anamnesis is of help in differentiation.

Tetanus neonatorum.—This disease may occur during the first few days of life, the source of infection being the umbilical wound. Trismus is a prominent feature, though the limbs may also be involved or the spasms may become generalized, usually, however, only after the muscles of the neck and pharynx have become affected. This progress is the opposite to what occurs in tetany. Moreover, tetany is exceedingly rare before the third month of life.

Meningitis.—In *epidemic cerebrospinal meningitis,* there may be rigidity of the neck, opisthotonos, hyperesthesia of the skin and of the muscles, and fever; and tetany may, very rarely, yield a picture resembling this. But in cerebrospinal meningitis due to meningococcus infection, the pain is not dependent upon the muscle spasms for its production, nor is it limited to the muscles actually in spasms. Moreover, there are no remissions of the muscular spasms such as are seen in tetany. The typical tetany signs (Erb's phenomenon, Trousseau's phenomenon) are absent in meningitis. Lumbar puncture reveals, in epidemic meningitis, the presence of polymorphynuclear leucocytes and of meningococci.

Tuberculous meningitis in children occurs most often between the third and the fifth years, whereas tetany in children occurs chiefly between the first and the third year. In tuberculous meningitis there is a long premonitory stage, which is absent in tetany. Spasms resembling tetany spasms are rare in tuberculous meningitis; and the headache, the vomiting, and the paralysis of the cerebral nerves, especially of those innervating the

eye muscles, direct the examiner's attention to the basilar meninges. In tetany, the pulse is accelerated; in tuberculous meningitis it is usually slowed and irregular. In meningitis, irregular breathing is observed; this is unusual in tetany.

It must be remembered, however, that the tetany syndrome may occur in the course of a tuberculous meningitis associated with general miliary tuberculosis. In one such case, at autopsy, Winternitz (now of Yale University) found miliary tubercles in a parathyroid gland!

Lumbar puncture should be done, if any doubt about the existence of tuberculous meningitis exist. The film in the fluid, the mononucleosis, and the presence of tubercle bacilli decide the diagnosis.

Katatonia.—The stereotyped attitudes seen in katatonic stupor might, by the uninitiated, be confused with the tonic spasms of tetany. The muscles once innervated in katatonia may preserve their innervation for hours, for days or even for weeks, unintermittently. The head may be inclined to one side, the legs may perhaps be crossed, the mouth may be projected snout-like, or the thumbs may be turned in.

But the mental state of the katatonic patient is characteristic (negativism, command automatism, grimaces) and, moreover, the marks of tetany (increased electrical excitability, facial phenomenon, leg phenomenon, etc.) are absent.

b. Conditions in Which Tonic Spasms that Involve Local Muscular Domains Occur

Facial Spasm.—When, in tetany, the spasms are limited to the muscles of the face and of the eyelids, their true nature might easily go unrecognized. Scheiber has reported a case in which facial spasms lasting for weeks were due to tetany, though no other spasms were present in the body. The differentiation among the different kinds of facial spasm that may occur is, as Chvostek points out, especially difficult, because clonic spasms of the face may occur along with tonic spasms in tetany.

Spasm of the Glottis.—Laryngospasm is one of the common symptoms of tetany in childhood and may be the only spontaneous tonic spasm exhibited. Most tetany children that suffer from laryngospasm also have rickets, and there has been much dispute as to whether the laryngospasm is due to the tetany or to the rickets. It is also known that laryngospasm may be a symptom in organic diseases of the brain (meningitis; sclerosis). The diagnosis of tetany with laryngospasm in children depends upon the demonstration of the existence of an increased electrical excitability of the motor nerves.

Spasm of the Diaphragm.—Spasm of the diaphragm is sometimes met with in tetany, but this form of spasm must be distinguished from asthma

and from hysterical spasm of the diaphragm. The general diagnostic survey should easily differentiate.

Cramps in the Calf Muscles.—These may be due to tetany, in which event other signs of tetany can also be demonstrated to be present. Cramps in the calves may also be due to other metabolic disturbances (uremia, gout, etc.).

Hysterical Contracture.—This may resemble the spasm of tetany very closely, but it is generally unilateral, whereas, in tetany, the spontaneous contractures are usually bilateral. Even bilateral spasm of the upper extremities and also of the lower extremities has been observed in hysterical persons and designated "hysterical tetany." Some of these cases were doubtless combinations of true tetany with hysteria, but if true tetany be present, one or more of the signs of latent tetany should be elicitable (Chvostek's phenomenon, Erb's phenomenon, etc.).

Occupation Cramps.—Cramps in the muscles concerned in the movements that pertain to certain occupations are manifested by some persons (writer's cramp, piano player's cramp, seamstress's cramp, telegrapher's cramp, shoemaker's cramp, cigarette roller's cramp, etc.), and may be mistaken for the spasms of tetany. The patients are neuropathic.

As a rule, these occupation cramps are independent of tetany; but shoemaker's cramp, especially, is most often due to tetany, as are the cramps that occur in carpenters and tailors. It has been suggested that the attitude in which the body is maintained during a large part of the day by these workmen causes disturbances of circulation in the neck and so leads to deterioration of function of the parathyroid glands. If an occupation cramp be really due to tetany, the specific signs of tetany can be elicited.

Myotonic Phenomena.—The occurrence of myotonic symptoms in tetany, and the occasional combination of tetany with true myotonia congenita have been fully described under symptomatology.

c. Myoclonias and Fibrillary Twitchings

Myoclonias.—In the myoclonias there are clonic contractions involving chiefly the muscles of the extremities and the trunk, the face usually escaping.

These clonic contractions affect muscles independently of synergisms. They are sometimes confined to a single muscle that cannot be independently innervated by the will, such as the musculus brachioradialis. Now myoclonic contractions are sometimes met with in tetany, but they seldom have the distribution of those seen in true paramyoclonus multiplex. Moreover, myoclonic tetany is accompanied by the other signs of tetany.

Fibrillary Twitchings.—Fibrillary and fascicular twitchings are sometimes observable in the muscles in cases of tetany and make one think of some lesion irritating the anterior horns or the motor nuclei of the cerebral

nerves. When these are associated with muscular weakness, or paralysis, they may be very confusing (see below: Motor Paresis in Tetany).

d. Tics and Habit Spasms

It is characteristic of the tetany contracture that the persistent tonic spasm lasts, usually, for hours or even longer. A tic is characterized, on the other hand, by short, violent movements, frequently repeated. Occasionally in tetany one sees spasms of brief duration that suggest a tic. Patients with tic can temporarily resist the impulse, though they suffer marked discomfort in doing so. The spasms in outspoken tetany cannot be controlled by the will. Moreover, motor tics and habit spasms are not associated with the other symptoms of tetany.

e. Convulsive States (Fits)

Fits, or convulsions, consist of violent motor discharges or explosions that are, as a rule, associated with disturbance of consciousness. When the fit is of cerebral origin, it may be psychogenic, as in hysterical attacks or in psychasthenic fits; or it may be toxic, or epileptiform (non-psychogenic) in nature.

General convulsions, or fits, are sometimes met with in tetany and are, apparently, sometimes actually due to the tetany itself. It must also be remembered that tetany may occur in combination with other diseases that cause fits. When tetany is demonstrably present, it may be exceedingly difficult to say whether a fit is due to the tetany or to some complicating disorder. Fits not due to tetany may closely resemble those that are due to it.

Hysterical Convulsions and Major Hysterical Attacks.—Hysterical contractures simulating the tonic contractures of tetany have already been referred to above, but hysteria may also be the cause of a general convulsive seizure that may be accompanied with loss of consciousness and have associated with it contractures that are suggestive of tetany. The influence of suggestion in producing, and in abolishing, the attacks is helpful in differential diagnosis. I am inclined to think that some of the cases reported as hysteria simulating tetany have been true combinations of tetany with hysteria. With so many criteria now available for the recognition of tetany and parathyroid insufficiency, there should rarely be any difficulty in deciding whether or not a true tetany exists in addition to hysterical phenomena.

Psychasthenic Fits.—These have been described by Oppenheim, Spiller, and others. They differ from both epileptic attacks and hysterical attacks, appearing as attacks of unconsciousness, with or without convulsive seizures, and often as equivalents of a psychasthenic anxious state. Some-

times a large number of "small attacks" may occur in a single day. If, in such patients, any of the tetany signs be present, the question of the exact origin of the fits might come up. The study of the patient as a whole and especially of his mental state, together with a search for the characteristic marks known as "tetany signs," will usually resolve the difficulty. The condition is rare anyway, and not likely often to be confusing.

Epilepsy.—Tetany can cause attacks that cannot be distinguished from the convulsions of epilepsy, and patients with true epilepsy may occasionally show one or more of the tetany signs when there is good reason to believe that tetany is not responsible for the convulsions. The relations of tetany to epilepsy have been fully described above under symptomatology (*q.v.*).

Puerperal Eclampsia.—Convulsions during and after childbirth may be due to tetany or, in cases of nephropathy, to uremia. The differential diagnosis is usually easy. In the nephropathic cases the presence of albumin and casts in the urine, the occurrence of edema, the content of the blood in rest nitrogen, and the phenolsulphonephthalein output, give the clews. In tetania gravidarum with eclampsia Chvostek's phenomenon, Erb's phenomenon and, often, Trousseau's phenomenon are demonstrable.

Eclampsia infantum.—Convulsions in children may be a part of the spasmophile diathesis (to which tetany belongs); or they may be due to organic brain diseases (congenital malformation of the brain, porencephaly, cerebral hemorrhage, cerebral sclerosis, cerebral syphilis, brain tumor, hydrocephalus); or they may be symptomatic of meningitis, or of the beginning of some acute infection (scarlet fever). Psychasthenic fits also occur in children.

The term *Spasmophilia, or Spasmophile Diathesis,* was introduced by Heubner to designate "a condition of excitability of the nervous system in early childhood accompanied by galvanic and mechanical hyperexcitability of the peripheral nerves and the tendency to tonic and clonic convulsive attacks." Spasmophilia is very common, indeed, in early childhood. At certain times of the year as many as thirty per cent of the sucklings will show signs of a spasmophile diathesis. Under spasmophilia are included not only (1) the majority of convulsive seizures in childhood and (2) attacks of laryngospasm but also (3) a condition, existing in a number of apparently healthy children, that can be recognized only by examining for mechanical and galvanic hyperexcitability of the motor nerves. Some regard the spasmophile diathesis as identical with the tetanoid state, or with latent tetany, and make the diagnosis of its existence in every child in which a kathodal opening contraction can be obtained with galvanic currents below five milliamperes in strength.

The three principal clinical symptoms of spasmophilia are (1) laryngospasm, (2) eclampsia infantum, and (3) tetany contractures (carpopedal spasms, arthrogryposis.) Some prefer to limit the term tetany to the third

condition only and thus make tetany a part of the more comprehensive spasmophilic group, whereas others believe that all the members of the spasmophilic group of conditions belong to tetany and, perhaps, to hypoparathyroidism. The tendency toward the latter view seems to be increasing.

2. Conditions (Other than Tetany) that May Simulate the Motor Pareses Sometimes Seen in Tetany

Though, in tetany, hyperkinetic signs are much more common than pareses, still undoubted cases of tetany exist in which there is marked weakness, either local or general, of the muscles. When these pareses of tetany are accompanied by fibrillary or fascicular twitchings, confusion with other diseases is easily possible.

Poliomyelitis.—If the motor pareses involve the extremities and are accompanied by fibrillary twitchings, poliomyelitis will of course be thought of in making a differential diagnosis, though the phenomena may, in reality, be due to tetany. If, on the one hand, one searches for other tetany signs and, on the other, makes a study of the cerebrospinal fluid, there will be no difficulty in distinguishing between the two diseases.

Progressive Muscular Atrophy.—This form of muscular atrophy with muscular paresis, whether it affect the muscles of the extremities or those in bulbar domains, might, in rare instances, be confounded with the motor pareses that sometimes follow tetany. In some cases of tetany, as we have seen, the paretic phenomena entirely overshadow the hyperkinetic phenomena. The latter may even be wholly absent. In tetany, however, there is no real muscular atrophy, and there is an increase of the galvanic excitability of the motor nerves, whereas this is absent in progressive central muscular atrophy.

Peripheral Neuritis.—Tetany has, occasionally, been confused with alcoholic and other forms of polyneuritis, which it sometimes closely resembles in its sensory phenomena and in the depression of the deep reflexes. The anamnesis and the careful search for tetany signs will differentiate between the two diseases.

Muscular Dystrophies.—In some cases of tetany there is marked paresis of the lumbar muscles and of the muscles about the hips, the patients exhibiting a wobbling gait very much like that seen in some forms of muscular dystrophy. Here, again, an analysis of the anamnesis, a study of the heredity and of the familial conditions, the consideration of the time of appearance of the phenomena, the examination of the trophic condition of the muscles (atrophies, pseudohypertrophies), and the weighing of the results of the electrical examination, will give adequate differential criteria.

Encephalitis and Encephalomyelitis.—Now that encephalitis lethargica is epidemic and many atypical cases are seen, in which hyperkinetic phenomena on the one hand or paretic phenomena on the other, along with myoclonias, fibrillary twitchings, fascicular twitchings and the like, are met with, the possibility of confusion of this disease with tetany should be kept in mind. An exact neurological examination will easily differentiate. Frequently, the results of a study of the cerebrospinal fluid will be decisive, though not always, for the fluid is often normal in encephalitis.

Myasthenia gravis.—In tetany accompanied by paresis and by great general weakness, myasthenia gravis may be suspected; but the peculiar fatiguability, the absence of tendency to spasm, the exhaustibility of the muscles by the electrical current (so-called myasthenic reaction), and the absence of any increase of the electrical excitability of the motor nerves are marks of myasthenia gravis, which, if absent, rule out this disease.

3. Conditions (Other than Tetany) That May Be Associated with Sensory Phenomena Resembling Those of Tetany

Acroparesthesias.—Cases of so-called "sensory tetany" occur, in which abnormal motor phenomena are almost absent, the patient complaining chiefly of paresthesias in the extremities. Similar acroparesthesias are met with under different conditions, especially at the climacterium, in the functional neuroses, and in several endocrine affections other than tetany. In pernicious anemia, also, it is quite common to meet with remarkable acroparesthesias in the fingers and toes dependent upon degeneration in the funiculi of the spinal cord.

Unless acroparesthesias can be shown to be associated with the signs of latent tetany, they should not be ascribed to tetany.

Arthritides.—Physicians in Vienna have reported that patients often come to them with a diagnosis of rheumatism, or of arthritis, when the true explanation of their symptoms is the existence of tetany. The confusion doubtless depends upon the peculiar drawing pains in the extremities, variable in localization and in intensity, that occur in tetany. When the pains are very severe and the hyperesthesia of the skin is marked, tetany may be mistaken for acute infectious arthritis or for acute articular rheumatism. There may be even swelling and redness of the hands in tetany.

It must not be forgotten that true tetany may be combined with true arthritis, the arthritis, just like any other infection, acting as a releasing factor for the attack of tetany. In the differential diagnosis one

falls back upon tests for mechanical and electrical hyperexcitability of the motor nerves.

Raynaud's Disease.—The sensory phenomena of Raynaud's disease may simulate those of tetany, but tetany signs are not present in true Raynaud and the local anemias and asphyxias are very characteristic. Weber has, however, suggested that Raynaud's disease may be a vasomotor tetany.

IX. Prevention of Tetany

If we are right in our belief that tetany often depends upon parathyroid insufficiency, three general principles may guide us in prophylaxis:—(1) we should avoid removal of, or injury to, the parathyroid glands in operations upon goiter; (2) we should avoid other conditions believed to favor parathyroid insufficiency; and (3) when a predisposition to tetany or a latent tetany is known to exist, the circumstances that may release an attack or cause an exacerbation of the disease should be avoided.

The operation for goiter has been so greatly improved that tetany from now on will but rarely occur after thyroid operations. Any operator may, of course, injure the parathyroids by accident, and, in a certain number of cases, the surgeon will be compelled to remove one or more of the parathyroids on account of malignant growth.

In the operation for goiter, resection is now done instead of total lobectomy, in order to protect the parathyroid glands and the recurrent laryngeal nerves and to preserve a slice of thyroid in case an operation has to be performed later, possibly by another surgeon, on the opposite lobe. In the resection of a lobe of the thyroid, the blood vessels undergo "ultraligation" (well beyond the origin of the parathyroid arteries). Ligation of the inferior thyroid artery is not practiced, and the wound is closed without drainage. W. S. Halsted (*e*) has fully described all the improvements in the operation in his recent monograph, "The Operative Story of Goitre" (Baltimore, 1920). In case a parathyroid gland is accidentally removed at operation and the discovery is made during the operation, it should be immediately transplanted (preferably along with a small slice of thyroid) into a preperitoneal pocket or at some other site where the graft may be expected to grow.

Avoidance of infection at the operation for goiter goes far toward preventing scar formation with subsequent injury to the parathyroids or to their blood supply.

We are much less well informed regarding methods of preventing the forms of tetany other than postoperative tetany. Why tetany is especially prevalent in certain places and not in others we do not yet know, and it is doubtful if much benefit would result from advising people to avoid living in tetany towns. Even when certain of the occupants of such a place

actually have tetany, we are not sure that the removal of these persons to another residence would be of any help. It might, perhaps, be advisable for persons known to have tetany, or a disposition to tetany, to go for a holiday, or for work, during the tetany months to some place in which tetany is neither endemic nor epidemic.

By controlling the other factors that are known to favor parathyroid insufficiency (certain occupations, infections, intoxications, faulty diet, maternity, gastro-intestinal disturbances), something may, perhaps, be done in the way of prevention. Shoemakers, tailors, carpenters, and seamstresses, who already have shown a disposition to tetany, might be advised to change their occupation and be warned against too sedentary a form of life, and especially against bending over of the head while at work and overuse of the hands.

Women known to be predisposed to tetany should avoid pregnancies. If pregnancy should inadvertently occur, the question of its interruption, if possible waiting for a time when the child is viable, might be considered. The tetany mother should be forbidden to suckle her own child; a wet-nurse should be obtained, or, where this is not possible, artificial feeding may be resorted to.

Experiments upon animals indicate that an excess of meat in the diet seems to favor the appearance of tetany. Persons predisposed to tetany should, therefore, limit their meat intake, living largely upon milk, eggs, cereals, vegetables and fruits.

All that we can do otherwise in the prevention of tetany in predisposed persons is to counsel them to live in the most rational way possible under the most favorable sanitary conditions, and to recommend that they avoid, especially, notoriously unfavorable factors (bodily overexertion, vicious body attitudes, exposure to cold, etc.).

Persons who have already had one attack of tetany will do well to pay strict attention to the above considerations.

X. Treatment of Tetany

The physician who treats tetany should keep in mind that he has to deal with a chronic disease, in the course of which acute exacerbations can often be called forth by a variety of releasing factors. As Chvostek (*d*) has emphasized, a therapy that is directed toward the acute attack of tetany only would not fulfill its mission. A rational therapy must strive to do away with the chronic disorder that underlies the outbreaks of tetany. This pathological disturbance consists, as we have seen, in a vice of metabolism, due in many cases at least to an insufficiency of function of the parathyroid glands. A rational therapy will, then, attempt either to restore the function of the parathyroid glands, or, if this be impracticable, to resort to a

substitution therapy. The route to follow in the parathyrogenous cases is obviously that of organotherapy, and to the progress that has been made in this direction we may now conveniently turn.

1. Organotherapy in Tetany

Three forms of organotherapy can be utilized: (1) substitution therapy, that is, the administration of parathyroid gland substance in one or another form to the tetany patient: (2) surgical transplantation of parathyroid glands into the persons suffering from tetany; and (3) endocrin therapy, with the use of products derived from glands other than the parathyroids.

Substitution Therapy.—Various forms of substitution therapy with parathyroid substance and parathyroid products have been tried. Moussu (1898) was able to arrest postoperative tetany in dogs by subcutaneous and intravenous injections of extracts of horse's parathyroid. He made extracts with sterile water and also extracts with glycerin, but preferred the former.

Vassale (*c*) (1905) introduced an extract of parathyroid glands, which he called parathyroidin. He asserted that it had a favorable effect upon tetany attacks in human beings. He did not, however, describe the method that he used in preparing the extract. Vienna physicians (von Frankl-Hochwart, Escherich) could not convince themselves that this parathyroidin caused any improvement in cases of tetany. According to Gussio, Vassale's parathyroidin produces in dogs and rabbits a pronounced, though temporary, tachycardia.

Vincent and his colleagues (1904-5) reported that they were unable to prevent the onset of symptoms after complete thyroparathyroidectomy by the use either of extract of thyroid or extract of parathyroid glands.

W. G. MacCallum (1909) injected an emulsion of four or five parathyroid glands of the cow, prepared aseptically, beneath the breast of a girl suffering from tetany after a thyroid operation. Seventy-two hours after the operation a violent attack of tetany occurred, the girl becoming rigid and perfectly helpless, with typical obstetrical hand, the feet extended, and the jaws tightly set. Several hours after the injection of the parathyroid emulsion there was complete relaxation of the rigid muscles and the patient fell asleep, to wake up the following morning apparently quite well. Four days later she had another severe attack, which was treated in the same way with, apparently, the same good results. After this, she had no more tetany symptoms, probably due, MacCallum thought, to recuperation of her injured parathyroid glands.

Berkeley of New York found that he could relieve promptly the symptoms of tetany in a man of 39 by administering orally capsules of fresh

ox parathyroid, ground up with sugar of milk. J. J. Putnam also reported a case of postoperative tetany in which the same preparation gave relief.

Berkeley and Beebe (*a*) in 1909 discovered that the active principle of the parathyroid gland lies in its nucleoproteid fraction and that it is destroyed by heating to 80° C. for half an hour. This nucleoproteid is most active when freshly prepared. It rapidly deteriorates when kept i solution, or in suspension, in the refrigerator. Freezing also destroys its activity. It is injured, too, by the juices of the digestive tract.

These experiments that show that the nucleoproteid is injured by heat, by cold and by digestion, made Berkeley and Beebe believe that the active principle of the parathyroid glands is a ferment.

Berkeley and Beebe asserted that their nucleoproteid relieves tetany, if given by the mouth, but that it acts much more quickly and effectively when administered subcutaneously or intraperitoneally. The globulin of the parathyroid glands contains, they maintained, no substances that combat tetany.

Since the above observations were made, numerous papers have appeared in the literature commenting upon the effects of parathyroid extracts in the treatment of tetany. Though relief seems to have followed their administration in the hands of some observers, others report having seen no benefit whatever. It must be remembered, of course, that tetany, left to itself, often disappears quickly, and it may be that some of the favorable reports following treatment with parathyroid extract, like those in which improvement has been said to have followed the administration of thyroid extract, can be accounted for simply by differences in the course of an extremely variable disease.

Organ Transplantation in Tetany.—The unsatisfactory results obtainable by administration of parathyroid gland substance and extracts of parathyroid glands led experimental physiologists and surgeons to try the effects of transplantation of the parathyroid glands themselves on the symptoms and course of tetany.

Some of these transplantations appear to have been made unwittingly before the relation of the parathyroid glands to tetany was known (Schiff, 1884; von Eiselsberg, 1892). These surgeons transplanted fresh thyroid gland into the peritoneal cavity, or into the abdominal fascia after thyroidectomy, and found that tetany was thus prevented. Removal of the transplanted tissue later was followed by fatal tetany.

Biedl transplanted isolated parathyroid glands of the dog and of the cat into the spleen and asserted that, after successful autotransplantation, the removal of the thyroid gland with all the adjacent parathyroid glands could be borne without fatal consequences. Though tetany sometimes appeared, it was but temporary. From one dog that for four months after the transplantation of parathyroids into the spleen had remained free from

tetany Biedl extirpated the spleen and the parathyroids it contained, and the animal then developed a severe tetany within twenty-four hours and died. Biedl found two parathyroid glands with their histological structure well retained in the spleen after its removal.

In several cases of transplantation of parathyroid glands into the spleen, Biedl did not obtain permanent relief from tetany, the animals finally dying of the disease. On postmortem examination of these animals, scar tissue was found at the site of implantation, the parathyroids having been completely absorbed.

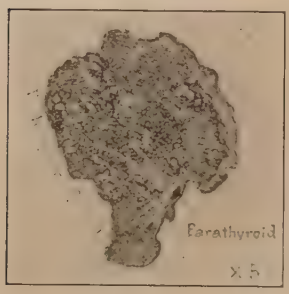
Biedl further asserted that in some dogs homoiotransplantation was as successful as autotransplantation. In these dogs, he first implanted into the spleen parathyroid glands (two to four) from other dogs, and a few days later extirpated the whole thyroid-parathyroid apparatus from the neck. The animals exhibited slight symptoms of tetany at first, but then remained for months without symptoms. The prophylaxis was not, however, permanent. Similar experiments to these of Biedl have been reported by Pfeiffer and Meyer, though they implanted the parathyroid glands into pockets in the rectus abdominis muscle of young dogs.

W. S. Halsted (*a*) (*b*) (*c*) (*d*) also made a long series of experiments with autotransplantation and isotransplantation of parathyroid glands in dogs. In some sixty animals he transplanted parathyroid glands, using the thyroid gland, the abdominal wall, and the spleen as sites for the implantation. Autotransplantation was successful in 61 per cent of the cases in which more than half of the normal parathyroid glands had been previously removed; but autotransplantation did not succeed, if the reduction of the dogs' own parathyroid glands had been less than this. He was never successful in grafting parathyroid tissue into a dog, if the animal's own parathyroids were all intact. He found that one autotransplanted parathyroid gland will entirely suffice to keep an animal in good health for months and even for years (Fig. 17). But he asserts that isotransplantation of the parathyroid glands in dogs invariably fails to yield grafts that live. The more recent experiments of Leischner and Köhler would seem to confirm these views of Halsted.

Halsted's studies made him skeptical, therefore, of the reported successes of Biedl, since that author asserted (1) that transplantation succeeds even without any previous loss of parathyroid glands; (2) that several parathyroid glands may by transplantation be made to grow and to function; and (3) that isotransplantation of the parathyroid gland in the dog is sometimes successful.

Answering these objections of Halsted, Biedl has argued that in his autotransplantation there is, in reality, a lack of functioning parathyroid gland at least for a time, namely, for the period that elapses between the time the parathyroid tissue is implanted into the spleen and the time it becomes vascularized. Biedl grants that parathyroid grafts grow more

quickly and better if a previous defect has been created. In his opinion, however, complete lack of parathyroids not only lessens the chances of the graft taking, but may prevent its taking entirely. No experimenter, he says, has thus far succeeded in making an implanted graft of parathyroid grow in a case of tetany appearing after total parathyroidectomy. Though Halsted had maintained that isotransplantation never succeeds anyway, and that, further, when several parathyroids are autotransplanted, not more than one will grow, Biedl assevers strongly to the contrary, at least as far



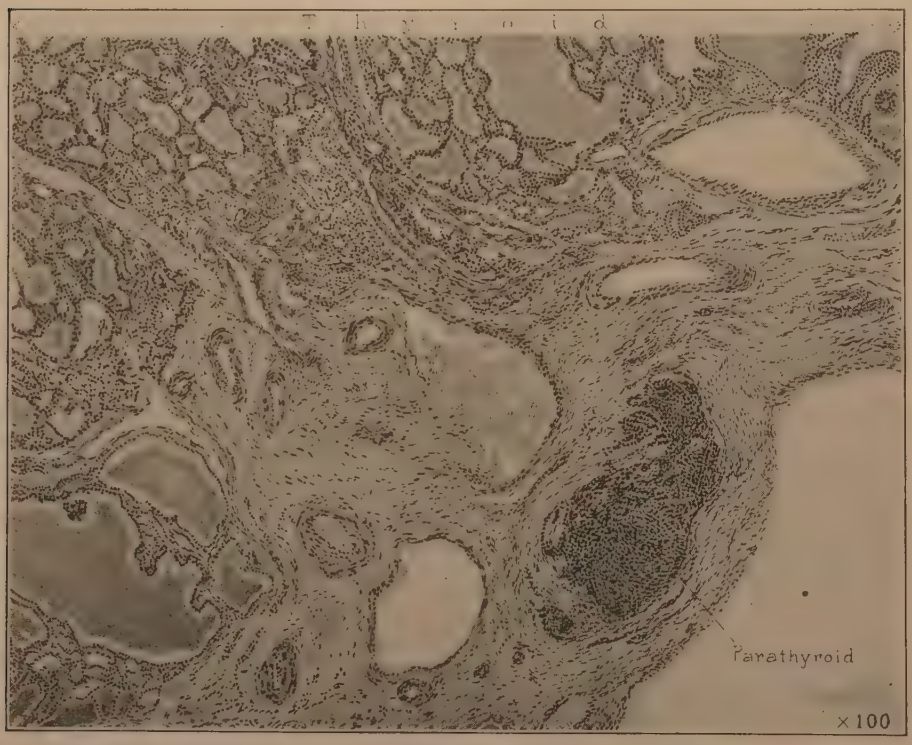


Fig. 17. Parathyroid autograft, approximately ¼ of a millimeter in diameter, which prevented tetany in a dog for 15 months. Three months after the removal of the tiny transplant the death of the dog occurred from hypoparathyroidism. (After W. S. Halsted, J. Exp. Med., 1912.)

as functionation and anatomical integrity for a limited time are concerned. He has, he asserts, several preparations of "foreign" parathyroids that, after implantation into the spleen or the abdominal muscles, had remained functionally active for from several weeks to several months; they present the picture of normal parathyroid tissue, showing signs of

regression and, at the same time, lively proliferation. Biedl has published a drawing of such tissue on page 112 of the second edition of his *Innere Sekretion.*

Other investigators have tried transplanting parathyroid gland by intravascular injection, and assert that the little emboli will grow and function, at least for a time. Thus, Landois (*b*) made autotransplantations in this way, injecting the external parathyroids (after extirpation of the internal); tetany was thus prevented in 7 out of 11 experiments. And Joannovics has also made intravascular isotransplantations of embryonic thyroid and parathyroid tissue in cats; he found that these isotransplantations would keep the animals alive for some time after total thyroparathyroidectomy, though they ultimately died of cachexia.

Implantations of parathyroid glands have also been made in rabbits, rats, and other animals. Cristiani, who has had a large experience with parathyroid transplantations in both rats and cats, states that, notwithstanding central necrosis of the grafts, he found normal parathyroid tissue two years after implantation in the rats and five years after implantation in the cats.

It would seem from these studies of transplantation of parathyroid glands in animals that the grafts rarely, if ever, develop into fully functioning organs. Absorption from the gland substance transplanted can, however, temporarily compensate for parathyroid insufficiency, and, perhaps, give accessory parathyroid glands a chance to hypertrophy, or injured parathyroid glands a chance to recuperate.

Halsted (*a*) in 1907 described at length his technic for the transplantation of parathyroid glands into the spleen of dogs. He also stated then that the thyroid gland apparatus in Graves' disease in human beings should serve admirably as a site for parathyroid transplantation. On several occasions, when operating for exophthalmic goiter, he transplanted to the opposite lobe, or into the isthmus, a parathyroid gland, the nutrition of which had been cut off or imperilled. Once a parathyroid that had been thus transplanted was subsequently and unintentionally excised.

Halsted early thought of parathyroid transplantation as a remedy in gastric tetany. When performing a gastro-enterostomy in one such case, he prepared for transplantation of a parathyroid gland into the spleen. Dr. MacCallum and Dr. Sowers obtained parathyroid glands for him from a cadaver (one hour after death). Unfortunately, a little carbolic acid came into contact with these parathyroids before the transplantation could be made, so he desisted from the attempt, though the spleen was in his hand and everything was in readiness for the transplantation.

In his report, made in 1907, Halsted stated that he had transplanted parathyroids into the thyroid gland and the spleen in seventeen dogs. In the spleen of each of three dogs as many as seven parathyroid glands were transplanted at one time.

Interesting reports of parathyroid transplantation in human beings have been made by a number of observers. Pool (*a*), of New York, reported, in 1907, the successful transplantation (to a woman with tetany) of a parathyroid gland removed from another patient who had died. He made two transplantations, one on March 1st, 1907, the other on the 17th of April. Parathyroid nucleoproteid was also administered subcutaneously. After one month the tetany symptoms had receded. It does not seem possible, in view of our present knowledge of viability, that these grafts really grew.

Von Eiselsberg appears to have been the first intentionally and successfully to transplant a living parathyroid gland directly from one living human being to another. The patient, a woman of 42, had suffered long from tetany, owing to a total strumectomy done years before. The graft (derived from a woman at operation for enucleation of a cyst from one lobe of the thyroid) was placed in a pocket of the rectus abdominis muscle, between the peritoneum and the fascia. This graft took, and the patient improved remarkably afterward. Though she still suffered occasionally from laryngospasm, the tetany otherwise disappeared, and the electrical excitability of the motor nerves returned to normal. Other successful transplantations of human parathyroids have been reported by Böse and Lorenz (1909), Danielson (1910), Krabbel (1911), and others.

How easily surgeons may mistake tissues that are not parathyroid tissue for the parathyroid bodies has been shown by Borchers (1912) of Tübingen, who found that of the transplants of supposedly parathyroid tissue in instances in that clinic, 8 were accessory thyroids, 1 was fat tissue and 1 was a lymph gland. Burk (1921) of Stuttgart has recently reported a case of postoperative tetany in which he transplanted at the operation a single parathyroid that had been excised with the goitre (autograft) and later attempted the transplantation of parathyroid glands (obtained from a cadaver thirty minutes after death) into the abdominal musculature of the patient (homoiotransplantation). For 4 days after the transplantation there seemed to be marked improvement; the spasms and convulsions ceased and Chvostek's sign and the Trousseau phenomenon became less easily elicitable. Burk felt sure that he had rescued his patient but on the sixth day the picture suddenly changed; the spasms increased, the respiratory muscles became involved, and on the eighth day the patient died with all the signs of a most severe tetany. It had seemed to him that the homoiotransplantation made 35 hours after the primary operation had relieved the symptoms for 4 days. At autopsy, however, he found that instead of parathyroid tissue he had transplanted only minute lymph nodules, whose size and color in the cadaver had deceived him. The temporary respite for 4 days must have been due, he thinks, to the autotransplantation. This respite, he believes, would not have been temporary except for the fact that an aseptic stitch abscess de-

stroyed this graft on the 6th day. Burk urges (1) that every goiter be examined closely immediately after removal for excised parathyroids, (2) that autotransplantation never be made near the operation wound, and (3) that before implanting supposedly parathyroid tissue, a minute portion of the graft be examined microscopically.

Even though it may be possible to cure tetany by transplanting parathyroid glands from one living human being to another, this form of therapy is greatly handicapped by the difficulties that will be encountered in securing the glands for transplantation. The danger to the donor may be grasped, if one recalls that the removal of a single parathyroid gland has been the cause of postoperative tetany in human beings. Two such instances have been reported by Böse and Lorenz. No wonder then that Biedl speaks of the excision of a parathyroid for this purpose *"mit Rücksicht auf den Spender als ein unheimlicher Eingriff."* And von Eiselsberg, who first successfully resorted to it, expressly warned us of the danger to the donor.

Despite the successes reported, it would yet seem doubtful whether homoiotransplantation is ever really successful. That autotransplantation occasionally succeeds there is good reason to believe.

Other Forms of Endocrin Therapy in Tetany.—Organotherapy with organ extracts other than parathyroid has also been tried for tetany. Thus, there are many reports in the literature of the beneficial effects of the administration of thyroid extract, especially in postoperative tetany. Many clinicians are skeptical of the good results that have been reported, but there are now so many observations on record that it would certainly seem worth while to try thyroid extract in tetania strumipriva if the symptoms cannot be sufficiently ameliorated by other measures.

The administration of pituitrin and of pituitary extracts seems also to mitigate the symptoms of tetany both in experimental animals and in man (Ott and Scott).

2. Pharmacotherapy in Tetany

Diuretics, purgatives, sedatives, and antacids have all been used in the treatment of tetany. In tetany in children, especially, emptying the bowels and bringing about diuresis and diaphoresis all seem to be helpful measures.

The use of sedative substances has played an important rôle in the treatment of tetany. Among the sedatives earlier employed, chloral hydrate, bromide of potassium, and antipyrin may be mentioned. Recently, since Netter's clinical observations and especially since MacCallum and Voegtlin's studies of calcium deficiency in tetany, calcium has been administered as a sedative in tetany and often with good results. MacCal-

lum and Voegtlin found that the injection of a solution of a salt of calcium into the circulation of an animal in tetany promptly checked all the symptoms, the animal returning to an apparently normal condition. Magnesium salts had a similar effect, but caused also an intoxication. These observers and many others (Parhon and Urechie, Berkeley and Beebe, Biedl, Stone, Bell and Martin, Ott) have made use of soluble calcium salts, administered orally, subcutaneously, or intravenously, in the treatment of tetany in human beings. These salts have been used in both postoperative and non-operative tetany and with and without the simultaneous use of parathyroid extract. Calcium therapy is doubtless capable of doing much to tide a patient over until the function of any remaining parathyroid glands can be improved, or, at any rate, until the causal vice of metabolism, whatever it may be, disappears. Calcium chlorid, calcium lactate, and calcium bromid are among the salts that have been used. In the severe forms of tetany, Moffit, of San Francisco, gives from three to five grams (45 to 75 grains) of calcium salt in from 300 to 400 cubic centimeters of normal salt solution intravenously. The injection may be repeated after twenty-four hours, if necessary. In milder attacks, fifteen grains of calcium lactate may be given three times a day by mouth.

Hyoscin and curare, which have sometimes been used as sedatives, are better avoided. Benzyl benzoate would seem worthy of trial.

3. Hydrotherapy and Thermotherapy in Tetany

During an acute attack of tetany a tepid bath often makes the patient feel more comfortable and helps to relieve the spasms. Applications of cold are, as a rule, harmful and exposure to cold may even precipitate an attack. Children subject to tetany should not be taken to hospitals or to dispensaries on cold days. On the other hand, Curschmann has produced prompt relief in some cases of tetany by the local application of cold. And Trousseau found applications of ice to the spine an advantage in some cases, though for laryngismus stridulus he applied a hot sponge over the trachea. Patients subject to tetany should live in an equable temperature and should wear wool next the skin, especially when exposed to the raw winds of the early spring months.

4. Electrotherapy in Tetany

Faradism and galvanism have been tried in the treatment of both acute and chronic tetany. They are of no value.

5. Mechanotherapy in Tetany

During acute tetany the patients should be kept at complete rest and no form of manipulative therapy should be employed.

After an acute attack has passed off, gentle general massage may be used cautiously as one of the general upbuilding measures.

6. Climatotherapy in Tetany

Seasonal influences, as we have seen, are very important in the incidence of the endemic-epidemic form of tetany. For patients who can afford it, residence in non-tetany districts would be advisable during the tetany months. Unfortunately, those affected by this form of tetany rarely belong to the classes that can easily defray the expense of seasonal migration.

7. Occupational Therapy in Tetany

Persons subject to tetany should not engage in occupations that require a sedentary life or much bending over of the head and upper part of the body (shoemaking, carpentry, sewing, tailoring, etc.). Open air occupations (agriculture, navigation, etc.) are far preferable for such persons.

8. Serotherapy in Tetany

On the theory that the tetany poison possesses the character of an antigen, Ceni and Vesta (1904) tried to immunize animals with the serum of an animal that has been parathyroidectomized, and asserted that, on injection of this immune serum, there was an immediate cessation of the acute phenomena, though the tetany was not cured.

Similar experiments have been made by H. Wiener and others, but a critical review of the results of serotherapy in tetany indicates that the method is of no value.

9. Dietotherapy and Other Measures Directed Toward Combating Tetany, Especially in Childhood

Great care should be taken to avoid digestive disturbances in tetany, since absorption of poison from the gastro-intestinal tract can act as a re-

leasing factor in latent tetany and give rise to the manifest syndrome. The diet in adults should be simple and bland, but it should be an all around diet, including a well balanced ration of proteins, carbohydrates, fats, salts, and vitamins. An excess of meat and of meat extracts (consommé) in the diet should be especially avoided.

In children presenting signs of the spasmophile diathesis, a proper diet, together with sunshine, light, and air, is important as a prophylactic and curative measure. During the suckling age, mother's milk is the best food, but if artificial feeding become necessary, cow's milk should be reduced to the smallest amount possible, and the amount of milk ingested should not exceed one third, or at most, one half litre per day. A moderate amount of carbohydrate should be given in the form of farinaceous foods or of malt soups. Older sucklings should be early accustomed to a mixed diet that, among other constituents, contains green vegetables and apple sauce. Large meals at any one time should be avoided in children that are subject to laryngospasm or to eclamptic attacks.

The pediatricians who treat tetany and the spasmophile diathesis recommend the use of phosphorus and codliver oil internally.

℞ Phosphorus 0.01
Oleum jecoris aselli 100.0
Sig:—One teaspoonful to be administered once or twice a day for several weeks at a time.

In administering calcium lactate to children, one gives 0.5 to 1 gram dissolved in 50 grams of water three times a day. L. F. Meyer has recommended the use of calcium bromide instead of calcium lactate.

Laryngospasm and eclampsia in children require the adoption of certain special therapeutic measures. A dose of castor oil, say a teaspoonful, should be given at once, and if there be much flatulence, the intestine may be emptied by enema and the procedure repeated in two hours. If the little patients are taking milk, it should be stopped at once, and for twenty-four hours only weak tea sweetened with saccharine or simply sterile water should be given. Salt solution should be avoided. The child should then be given human milk by a wet-nurse if possible; otherwise, gruels containing rice or oatmeal slightly sweetened may be fed. After four to six days of this treatment, the mixture of phosphorus and codliver oil above mentioned may be begun. Then only dare one cautiously add a little cow's milk to the diet, say 50 grams per day at first, gradually increasing the amount if severe laryngospasm or convulsions do not recur. One must be willing to let the child go without any gain in weight for several weeks, if necessary.

In severe eclamptic attacks, especially when they are often repeated, we have to depend upon tepid baths, colonic irrigations, cold compresses to the forehead, and, when necessary, chloral hydrate, best administered per rectum, 0.5 gram at a dose for sucklings, repeating the dose if nec-

essary. The drug, if administered by mouth, should be given in much smaller doses (Ibrahim). If laryngospasm threaten life, chloral should certainly be used. Chloroform inhalations can usually be dispensed with.

It is said that a lumbar puncture will sometimes stop rapidly recurring convulsive attacks in children. A little sodium bromide three times a day, given for two or three days, may lessen the tendency to laryngospasm.

Children subject to laryngospasm or to eclampsia should be kept perfectly quiet. Excitement or fright may precipitate an attack. Horsehair pillows, instead of feather pillows, have been advised, or the head may be kept on a head ring. Injections of camphorated oil may be given, if a quick stimulant should be required.

When a severe attack of laryngospasm occurs, the parent and nurse should first wait quietly. If the child does not soon begin to breathe, it may be sprinkled with a little cold water; and if the attack continue, the base of the tongue may be pressed down with the finger. Should this not prove sufficient, an injection of camphorated oil should be given, after which attempts to aid by artificial respiration may be necessary. The resistance to respiration may be insuperable, the pathologically closed glottis allowing no air to go either in or out. The moment the child inspires, making the characteristic sound that accompanies this, it is best to stop all further measures, so as to avoid bringing on a new spasm. Only when the breathing does not become regular does one continue artificial respiration. Intubation or tracheotomy comes nearly always too late, for death occurs from failure of the heart rather than from asphyxia. Some pediatrists have suggested continuous intubation of threatened children during days of greatest danger. Death is, fortunately, relatively rare from laryngospasm, though it does occasionally occur.

Brown and Fletcher, of Toronto, lay great stress upon the danger of the use, by children predisposed to tetany, of foods that have been superheated and that contain a high percentage of carbohydrates (especially proprietary foods). They believe that such a diet upsets the balance of the body salts, causing retention of sodium and potassium (the irritating salts) and loss of calcium and magnesium (the sedative salts). Mild diuresis, mild purgation, and correction of the diet will, they think, quickly bring about improvement.

10. Surgical Therapy other than Organ Transplantation in Tetany

When the special symptomatology and the prognosis of tetany associated with disease of the gastro-intestinal tract was discussed (*vide supra*),

the cures obtainable by surgical interference in this form of tetany were referred to. Tetania gastrica treated by medical measures only has a very bad prognosis.

In other forms of tetany, however, surgical measures other than organ transplantation should, as far as possible, be avoided. Even so simple an operation as dilatation and curettement of the uterus has been known to precipitate an acute attack of tetany.

(b) Parathyropathies Other than the Hypoparathyroidism of Tetany

Several parathyrogenous syndromes other than tetany have been mooted by clinicians, but the evidence that disturbance of parathyroid function is responsible for these syndromes is far less convincing than that in favor of the origin of tetany in hypoparathyroidism. Certain diseases of the bones (osteomalacia, Paget's disease) and certain diseases of the central nervous system (Parkinson's disease, Thomsen's disease, myoclonia, chorea minor, myasthenia gravis, and hyperparathyroid psychosis) have been attributed by one or another to hypofunction, hyperfunction, or dysfunction of the parathyroid glands. Finally, the relations of chronic renal disease to hyperplasia of the parathyroid and of the latter to the deposition of masses of lime salts in the body are worthy of consideration.

I. Osteopathies of Postulated Parathyropathic Origin

Osteomalacia.—In this rare disease, known also as *mollities ossium* and *spondylolisthesis,* a softening of the bones of adults, not unlike that seen in rickets in childhood, occurs. Women (in the reproductive period) are more often affected than men. The patients tire easily and suffer from severe pains in the back, hips, or extremities, especially on movement. Marked distortions of the bones result from the effect of the body weight upon the softened skeleton. The deformities of the pelvis due to preceding osteomalacia are among the difficulties encountered by the obstetrician. During the active stage of the disease there is difficulty in walking, weakness of the legs, and often adductor spasm of the thigh muscles. The nervous system often suffers also, the patients becoming forgetful, apathetic, or irritable. Pregnancy is often responsible for exacerbations of the disease. When males are attacked (*virile osteomalacia*), it is the bones of the spine and of the extremities that are mainly

affected, rather than those of the pelvis. The disease may occasionally occur in childhood (*infantile osteomalacia*) or in old age (*senile osteomalacia*).

For the diagnosis, the characteristic röntgenograms of the bones and the adductor spasm in the thighs are helpful marks.

McCrudden and Fales, who have studied the mineral metabolism in osteomalacia, assert that there is a negative calcium balance. In the bony tissues themselves, the calcium content is greatly decreased, though the magnesium content and the sulphur content may be increased, owing to the presence of much newly formed, but uncalcified, osteoid tissue. Zuntz found an increase of the phosphoric acid of the feces in osteomalacia.

It was probably the disturbed calcium metabolism in osteomalacia that directed attention to a possible parathyrogenous origin of the disease. Erdheim studied the parathyroid glands at autopsy in five cases of osteomalacia and found hyperplasia of the parathyroid secreting tissue in all the cases except one. Enlargement may affect one gland only, though in the other glands he could demonstrate, on histological examination, multiple small hyperplastic foci. He attributed the hyperplasia of the parathyroid tisue to an increased call upon the parathyroid function in one form of osteomalacic intoxication. In a later publication Erdheim described parathyroid changes, usually hyperplastic, sometimes neoplastic, in still other cases of osteomalacia.

The studies of Schmorl upon the parathyroid glands in four cases of osteomalacia revealed no changes at all in three of the cases, though he admitted that in one case a tumor of the parathyroid was present.

Erdheim's view has been supported by Strada, who found enlargement and tissue hyperplasia of the parathyroid glands in a single case of osteomalacia, and by Bauer, who also observed an adenoma in one parathyroid gland and hyperplastic focal changes in the others in an osteomalacic cadaver.

Though these pathological changes in the parathyroid glands in osteomalacia merit careful consideration, it would seem probable that osteomalacia is more closely related to diseases of the gonads than to disturbances of parathyroid function. In favor of the gonadal relationship of osteomalacia is the improvement that is said to follow oöphorectomy and castration in this disease. For reviews of the endocrin origin of osteomalacia, the reader is referred to the articles of Marinesco, Parhon and Minea (1911), of L. Bernard (in Gilbert & Thoinet's System, 1912), and of Sellheim (1913).

Paget's Disease.—In another rare osteopathy, namely, *Paget's disease,* known also as *osteitis deformans,* or *senile pseudo rickets,* a parathyrogenous origin has also been suggested.

The disease rarely appears before the fiftieth year of life. It begins insidiously with "rheumatic" or "neuralgic" pains in the bones and grad-

ually leads to characteristic deformations (ape-like appearance, bowing of the legs forward and lateralward, enlargement of the skull and of the clavicles, cervicothoracic kyphosis, violin shaped body, and enlargement of the lower aperture of the thorax). The stature of the patient may be reduced by as much as 13 inches (Osler). Chronic bronchitis and myocardial insufficiency are common complications in the later stages. E. A. Locke, of Boston, has emphasized the extreme atherosclerosis that occurs in this disease. The large arteries of the extremities are often seen calcified in röntgenograms, which also reveal a peculiar cottonwool-like change in the diaphyses and epiphyses of the long bones.

The disease sometimes affects several members of the same family, a fact brought to my notice by Dr. Marie Ingram of Baltimore, who permitted me to show at my clinic several members of such a family.

The etiology and pathogenesis of Paget's disease are still obscure, though two observations, at least, are suggestive of an endocrin, possibly of a parathyrogenous, origin. Thus, Askanazy in one instance observed a tumor, presumably of parathyroid source, attached to the left lobe of the thyroid, and Higbee and Ellis have described absence (?) of the parathyroid glands and of the thymus together with extreme atrophy of the thyroid gland, in another case. The mineral metabolism in Paget's disease has been examined by Da Costa, Funk, Bergheim and Hawk (1915).

II. Neuropathies of Postulated Parathyropathic Origin

Parkinson's Disease.—This disease, occurring usually in later life, and known also as paralysis agitans, is familiar to every practitioner. The peculiar rigidity of the body musculature, the characteristic attitude with the head and trunk bent forward, the arms adducted and flexed, and the legs slightly bent at the knees, the slow, coarse tremor (especially the pill-rolling movement of the thumb and forefinger), the facial "mask," the slowed movements and disinclination to movement, the disturbance of the finer movements (buttoning and unbuttoning), the peculiar gait (with propulsion, retropulsion, and festination), and the micrographia are marks that, once recognized, are not likely to be overlooked by any alert diagnostician.

In Parkinson's disease the functions of the extrapyramidal motor neurons are markedly interfered with, and J. Ramsay Hunt, of New York, has called attention especially to the degenerations that are demonstrable in this disease in the cell bodies of neurons situated in the globus pallidus.

As early as 1904, H. Lunborg had suggested that paralysis agitans may be due to a hypoparathyroidism.

In 1905, Berkeley asserted that the administration of parathyroid preparations would relieve the symptoms in Parkinson's disease, and since then many clinicians have tested this therapy, some with apparent success, others with failure. In my own experience with a number of cases, I have not been able to convince myself that any real benefit followed the administration of parathyroid substance, though Berkeley, in later reports, assevers that there was striking improvement in about 65 per cent of his large series of cases from the continuous oral administration of Beebe's parathyronucleoproteid. Roussy and Clunet (*a*) saw no benefit from parathyroid treatment of Parkinson's disease; indeed, they assert that their patients were made distinctly worse by it.

The parathyroid glands in Parkinson's disease have been studied at autopsy by a number of observers. Camp and Berkeley described pathological alterations in these glands, though Erdheim and R. L. Thompson, in the glands of their cases, could discover no anatomical lesions. Alguier studied four cases; in one, he observed changes intermediate between those of hypertrophy with copious colloid formation and those of atrophy; in another, he found vacuolization of the cells and marked eosinophilia; and, in the two other cases, there was atrophy of, and fatty changes in, the cells.

Very careful studies of the parathyroid glands in Parkinson's disease have also been made by Roussy and Clunet. In four cases that had been studied exhaustively clinically before death, they found the parathyroid glands definitely enlarged when compared with the glands at 100 autopsies on non-Parkinsonian cases. In the enlarged glands they demonstrated histologically a simple hyperplasia with increase of colloid, together with large numbers of acidophile cells. These authors interpret these findings as evidence of a hyperfunction of the parathyroid glands in Parkinson's disease, though they admit that the disease may be either a result or a cause of the hyperparathyrosis. They suggest that, possibly, both the Parkinson's disease and the hyperplasia of the parathyroids may be results of some unknown cause of a still larger process. The observations of Roussy and Clunet led Haberfeld and also Marañon (*a*) to study the parathyroid glands after death in cases of Parkinson's disease. These investigators assert, however, that they could discover no changes pointing either to a hyperfunction or a hypofunction of the glands.

Thomsen's Disease.—In this rare familial and hereditary disease, first clearly described by J. Thomsen (1875-76), and known also as *myotonia congenita,* the characteristic marks are (1) enlargement of the muscles, and (2) interference with voluntary motion, due to a rigidity that sets in on attempts to make movements. The mechanical excitability of the muscles is increased. On electrical examination, the myotonic reaction of Erb (*My R*) is met with; there is slight depression of galvanic excitability of the motor nerves; but the direct galvanic muscular irritabil-

ity is increased, though only closure contractions occur and AnCC is usually greater than KCC. The striking feature is the slow tonic character of the muscular contractions and their persistence.

The manifold relations of tetany and myotonia have been exhaustively discussed in the article by von Orzechowski (*vide supra*). The occurrence of a case of myotonia in a family in which cataracts were prevalent has been observed by Fearnsides (1915), and this is suggestive of a relationship to chronic tetany.

Interesting clinical observations on Thomsen's disease have been made by Johnson and Marshall (1915), and the metabolism of the disorder has been examined by Rosenbloom and Cohoe (1914).

Lundborg (*b*) (1904) suggested that Thomsen's disease, as well as Parkinson's disease and certain myoclonias, might be due to a parathyropathy, probably hypoparathyroidism. But thus far there would seem to be no evidence of this on the pathological-histological side.

Myoclonia.—Lundborg (*b*) (1904) placed myoclonias, and especially myoclonic epilepsy, in the hypoparathyroid group of neuropathies, apparently chiefly, if not entirely, on speculative grounds. I have been unable to find anything in the bibliography confirmatory of Lundborg's view.

Chorea Minor.—Haberfeld, in two cases of chorea minor, observed circulatory changes in the parathyroid glands, a fresh hemorrhage in one case, marked congestion in the other, and suggested that these changes pointed to a possible relationship of chorea minor to lesions in the parathyroid glands.

Myasthenia Gravis.—This condition, known also as *asthenic bulbar paralysis,* or the *Erb-Goldflam syndrome,* is characterized by a quick fatiguability of the muscles, manifesting itself on chewing (dysmasesia), on speaking (dysarthria), on swallowing (dysphagia), and on making other oft repeated movements. There are no sensory disturbances. The condition is subject to the most marked remissions and exacerbations.

On electrical examination, a characteristic myasthenic reaction, well described by Jolly, appears; when a tetanizing faradic current is applied to either motor nerve or muscle, and is repeated at intervals of a second, the muscular contractions grow feebler with the successive stimulations, until they finally disappear, though the muscle may regain its normal excitability after a short period of rest.

Lundborg (*a*) (1904) suggested that myasthenia gravis may be due to a hyperthyroidism and Chvostek (*c*) (1908) supported this view, urging that the symptoms in myasthenia gravis are diametrically opposite (like the negative contrasted with the positive in a photograph) to those of tetany. If tetany is due to hypoparathyroidism, it is reasonable, Chvostek stated, to assume that myasthenia gravis is due to hyperparathyroidism.

This view, sometimes referred to in the bibliography as the Lundborg-

Chvostek theory of the origin of myasthenia gravis, has not gained general acceptance. It is out of accord (1) with the pathological-anatomical studies of Haberfeld, who pointed out (a) that in the many cases of hypertrophy of the parathyroid glands and of tumors (adenoma, carcinoma) originating in these glands no signs of myasthenia have ever been observed, and (b) that in two cases of myasthenia gravis examined by him at autopsy, he could discover no changes pointing either to hyperfunction or to hypofunction of the parathyroids; (2) with the experimental studies of Biedl on dogs and those of Iselin on rats, in which a hyperparathyrosis produced by implantation of parathyroids gave rise to no myasthenic symptoms; and (3) with the experimental studies of Uhlenhuth, who found that thymus substance fed to *Amblystoma* will give rise to tetany (and in myasthenia gravis there is not only a persistent thymus but also, as Weigert demonstrated, an infiltration of the muscles themselves with thymic tissue).

Hyperparathyroid Psychosis.—Roger Morris (1915-16) has described an interesting psychosis that appeared in a woman suffering from Parkinson's disease, to whom parathyroid substance had been fed, partly in the form of fresh ox parathyroid, partly in the form of desiccated parathyroid gland, over a long period. After about a year of this treatment the patient began to fail and the signs of a peculiar psychosis developed. The patient became disoriented as to time, grew indifferent to her surroundings, lost interest in everything, became forgetful, negative, restless, sleepless, and irrational, and exhibited signs of auditory hallucinations, loss of sphincter control, anorexia, marked tachycardia and irregular menstruation.

Morris interrupted the parathyroid medication and treated the patient with wet packs, veronal, and tincture of nux vomica. Sleep was soon restored, the sphincter control was regained by the patient, and her mental state began to improve. But 17 days after stopping the parathyroid treatment, the patient developed signs of tetany spasm (?), though Trousseau's sign and Chvostek's sign could not be elicited. On administration of calcium lactate and a little parathyroid, the signs of tetany disappeared. At the end of three months, the mental state had become normal, though the patient had amnesia for the last four months of her psychosis and for the first two months of her convalescence.

Morris recalled that Berkeley (1913) had observed nervousness and insomnia following parathyroid treatment and that Salvioli and Carraro had asserted that parathyroid substance is toxic for the heart muscle. In view of these and his own observations, Morris suggested that there may be fairly definite clinical syndromes that are due to parathyroid intoxication, that is, to hyperparathyroidism.

III. Hyperplasia of the Parathyroid Glands in Chronic Renal Disease

As early as 1904, W. G. MacCallum (*a*) had reported a case of "tumor" of the parathyroid in a young person with renal disease, and suggested that the renal disease might possibly be the cause of the enlargement of the parathyroid. Cameron and Fletschner some years ago associated juvenile osteomalacia and infantilism with primary nephritis.

Enlargement of the parathyroid glands, apparently due to hyperplasia, has been described in ten cases of serious renal disease by H. Bergstrand. Bergstrand concluded that the hyperplastic tissue in the parathyroids in renal disease consists almost entirely of chief cells free from fat (or poor in fat) and devoid of colloid. In some of his cases of enlargement of the parathyroids in Bright's disease there was a circumscribed growth surrounded by apparently unchanged parathyroid tissue instead of a general hyperplasia.

Bergstrand states that no parallelism between the degree of the uremic symptoms and the enlargement of the parathyroids could be recognized, and in none of his cases could osteoporosis or osteomalacia be made out. In several instances there was a good deal of lime deposit, however, in the kidneys.

Certain other observations bearing upon the relations of renal disease and parathyroid function have been reported. Thus Larsson of Stockholm found an increased galvanic excitability of the motor nerves in acute nephritis. And Harbitz has reported a case of adenoma or struma of the parathyroids associated with nephritis and with a deposit of lime in the kidneys. He was uncertain whether the renal disease or the deposit of lime was primary.

During the present year (1921), Thomas and Wentworth of Clifton Springs have shown me x-rays and autopsy material from a remarkable case that illustrates well the relationship of hyperplasia of the parathyroid glands to chronic renal disease. The patient, a young man of 21, suffered from a severe nephritis at the age of 11. He died at the age of 21. Some months before death, large lime deposits appeared in the tendon sheaths and bursæ in various parts of the body, and an extensive arteriosclerosis with chronic arterial hypertension developed. The most extensive calcification of all the smaller peripheral arteries occurred. During life, x-rays revealed these calcifications of the arteries in the extremities, and especially in the voluntary muscles. At autopsy, röntgenograms were made of the tongue, of the heart and of the various internal organs and these revealed the most extensive calcification of all the smaller arteries. A certain decalcification of the bones similar to that seen in osteitis fibrosa was demonstrable in the x-ray plates and at autopsy the

bones were found to be soft; for example, the bones of the skull could be cut through with a knife. The kidneys were very much contracted. The large mineral deposits in various soft parts were found to consist of calcium carbonate and calcium phosphate. During life there was marked retention of certain of the urinary constituents (uric acid, non-protein nitrogen), in the blood. This case of Thomas and Wentworth's is so far as I know unique in medical literature.

SECTION IV

The Hypophysis Cerebri and Its Diseases

Anatomy, Embryology, Comparative Anatomy, and Histology of the Hypophysis Cerebri . . . . *E. V. Cowdry*

Anatomy—Terminology—Gross Morphology and Relations—Blood Supply—Lymphatics—Innervation—Embryology—Lobus Anterior—Lobus Posterior—Growth and Development of Various Parts—Early Endocrin Function of the Hypophysis—Comparative Anatomy—Histology—Pars Anterior Propria—Cell Types—Cytology—Pars Intermedia—Cytology—Pars Nervosa. (From the Anatomical Laboratory, Peking Union Medical College.)

Anatomy, Embryology, Comparative Anatomy and Histology of the Hypophysis Cerebri

E. V. COWDRY

NEW YORK

Anatomy

The word "hypophysis" is derived from the Greek, ὑπό, under, and φύειν, to grow, and is very appropriate from the standpoint of development. The older term "pituitary," on the contrary, comes from the Latin, *pituita,* clammy moisture, and was originally used to indicate the belief that the gland poured out a mucous secretion into the nasal cavity. The name is variously employed with reference to the whole organ and the anterior lobe only.

Terminology.—The following terminology will be used in this account:

Hypophysis pharyngei
  Canalis craniopharyngeus
Hypophysis cerebri
  (a) Lobus anterior
    Pars anterior propria
    Pars intermedia
    Pars tuberalis
  (b) Lobus posterior
    Infundibulum
    Pars nervosa
Parahypophysis

Gross Morphology and Relations.—The hypophysis is a small body weighing in adult males and nulliparæ about sixty-five centigrams. It is oval in shape, being about one centimeter long, one to one and a half centi-

meters broad, and one-half to one centimeter thick. During pregnancy it increases greatly in size, chiefly in the vertical and lateral diameters.

Relations.—The general relations of the hypophysis to the struc-

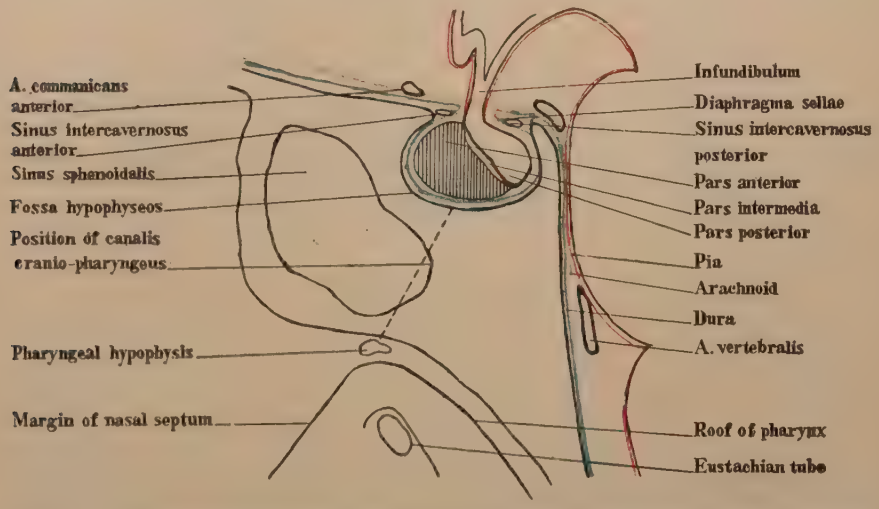


Fig. 1. Diagram showing the relations of the human hypophysis in median sagittal section. Dura, blue; arachnoid, yellow; and pia, red.

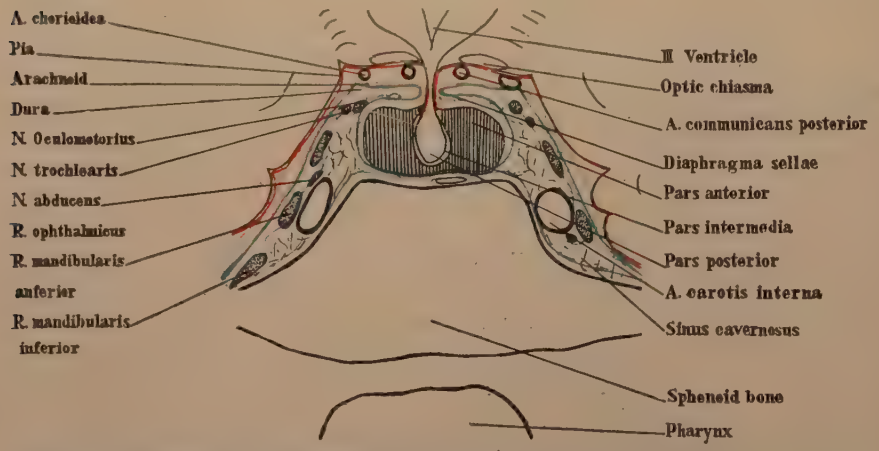


Fig. 2. Diagram of a transverse section of the human hypophysis. Dura, blue; arachnoid, yellow; and pia, red.

tures at the base of the skull are illustrated in Figs. 1 and 2. It is attached above to the hypothalamus by the infundibular stalk and is lodged in the sella turcica of the sphenoid bone. The chief variations in the shape of the sella turcica, and their importance from an operative standpoint are considered by Lewis. It will be seen from the diagrams

(Figs. 1 and 2) that the infundibular process, as it enters the sella turcica, is closely surrounded by the diaphragma sellæ, which is formed by a fold of the dura mater. The dura mater continues ventrally and lines the entire sella turcica, being closely adherent to the bone. The relations of the arachnoid are variable. It is usually reflected from the infundibulum at the diaphragma sellæ, but it occasionally extends further ventrally and partially encloses the hypophysis as it lies in the sella. When this is the case, there is greater danger of meningitis through opening the subarachnoid space during operations (Lewis).

Lobes.—The two lobes can easily be distinguished in the gross. The anterior lobe is larger and firmer in consistency and partially encloses

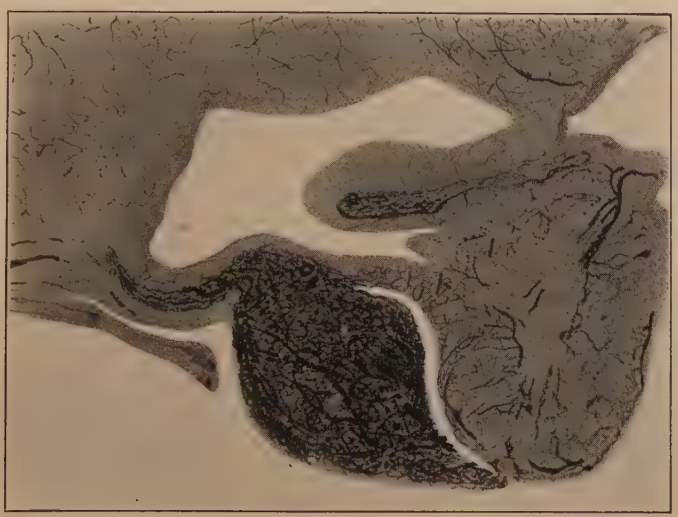


Fig. 3. Median sagittal section of injected hypophysis showing high vascularity of the anterior lobe as compared with the posterior lobe. (From Schafer, after Herring.)

the posterior lobe in a hilus-like depression in its caudal surface. On section it becomes apparent that the two lobes are also quite different in color; for the anterior lobe has usually a reddish tint, owing to its relatively high vascularity (Fig. 3), while the posterior lobe is often greenish yellow, depending upon the amount of contained pigment. On close examination of the anterior lobe, it is possible to define the limits of the pars intermedia, which is a thin epithelial layer between the anterior lobe proper, in front, and the posterior lobe, behind. The pars tuberalis, which is so distinct in lower forms, is only represented in man by an inconspicuous prolongation of the tissue of the anterior lobe along the infundibulum in the direction of the tuber cinereum, hence the term, "tuberalis."

Blood Supply.—The blood supply of the hypophysis springs from two sources, from the internal carotids as they are passing through the caver-

nous sinus, and from the circle of Willis. The internal carotid arteries give off very delicate branches, which run to the anterior lobe, and, according to Mudd, to the posterior lobe also. Twigs from the circle of Willis run downward with the pia mater which surrounds the infundibulum, and supply the posterior lobe. Dandy and Goetsch, working with the dog, have found that the pars intermedia also receives blood from the circle of Willis, so that a collateral circulation obtains between the anterior and posterior lobes, which, in their opinion, is "probably sufficient to preserve the function of at least the adjoining portion of either lobe, if its individual blood supply is cut off." Pending detailed information, we must bear in mind that a similar condition may exist also in man.

There is a marked difference in the vascularity of the lobes, which is well illustrated in Fig. 3. The pars anterior propria, in injected specimens, looks like an almost solid mass of contorted blood vessels. The pars tuberalis, when it is present, is said to be still more highly vascular. The blood in the different parts of the hypophysis seems to intermingle freely. In the sheep arterioles may be seen passing directly between the pars intermedia and the pars nervosa and between the pars tuberalis and the tissue of the infundibular stalk. The capillaries in the anterior lobe are large and sinusoidal and come into very intimate contact with the secreting cells. All the veins from both lobes discharge into the circular sinus.

Lymphatics.—Lymphatics are often described in the hypophysis, particularly in the anterior lobe, in connection with the discharge of secretion; but the exact method of drainage from the hypophysis remains to be worked out.

Innervation.—Our knowledge of the nerve supply in man is very scanty. Dandy, working again with the dog, finds that the nerves originate in the carotid sympathetic plexus and follow the arteries. He considers them to be for the most part sensory, not vasomotor, as one would naturally expect. The possibility of the existence of efferent fibers, running to the gland, is indicated by Shamoff's claim that he has been able to cause secretion of the hypophysis in the cat by stimulation of the superior cervical ganglion of the sympathetic.

Embryology

Lobus Anterior.—The anterior lobe is developed from an ectodermal pouch, called the pouch of Rathke, which grows upward under the brain from the stomodeal epithelium. In lower forms it is possible that there may be also an endodermal contribution from the fore gut, known as the pouch of Seessel. About the fourth week Rathke's pouch comes

into contact with the infundibular process, which is a downgrowth from the floor of the third ventricle, and which ultimately forms the posterior lobe. For convenience of description, we may divide Rathke's pouch into three parts, cranial, intermediate and pharyngeal.

Structures from the Cranial Portion of Rathke's Pouch (Pars Anterior Propria, Pars Intermedia, and Pars Tuberalis).—The cranial portion of Rathke's pouch usually becomes completely separated from the pharynx by the growth of the base of the skull and the formation of the sella turcica. A good account of the histogenesis is given by Tilney from whom I quote. In an embryo of twenty millimeters Rathke's pouch is in the form of a closed sac, somewhat flattened anteroposteriorly.

The anterior wall is destined to give rise to the anterior lobe proper; the lumen of the cleft often persists in the adult hypophysis, and the posterior wall develops into the pars intermedia. The cells constituting the anterior wall multiply rather more rapidly than those in the posterior wall, and become arranged in cords which are very noticeable in a twelve weeks' fetus. During the fifteenth week the cell cords become for the most part rearranged into acinus-like clumps. At this stage, the cells are all of the basophilic variety. There are indications that cells of the posterior wall penetrate into the neighboring infundibular process. Connective tissue elements from the diaphragma sellæ migrate into the interior of the gland. The posterior or intermediate portion begins to extend upward along the infundibular stalk, and probably gives rise to the tissue which has been recently called the pars tuberalis (Tilney(*a*)). In a human fetus of eight months the anterior and intermediate lobes are characterized by their extreme vascularity and by the deposition of colloid material in the cleft. Acidophilic cells make their first appearance during the ninth month of development. Their origin is not clear. The regional distribution of the various cell types will be discussed later (p. 714).

Accessory Hypophysis.—Occasionally the cranial anlage splits up at an early stage, with the result that small accessory glands develop, which, like the parent gland, are usually confined to the sella turcica. These accessory glands, when formed, are often fully differentiated and must be regarded as potential sources of internal secretion. The parahypophysis, described by Dandy and Goetsch in dogs, belongs in this category.

Little clusters of squamous epithelial cells have been found in the hypophysis by both Erdheim and Lewis, which have a marked tendency to tumor formation. Lewis remarks upon the fact that these misplaced fragments of buccal epithelium usually occur in the infundibulum and the adjacent portion of the anterior lobe.

Structures from the Intermediate Portion of Rathke's Pouch (Canalis Craniopharyngeus).—While the intermediate portion of the pouch usually disappears completely with the development and ossification of the

sphenoid bone, recent investigations have shown that its position is marked, in quite a large proportion of adult skulls, by a bony canal, the canalis craniopharyngeus, and a case is on record in which the hypophysis occupied this canal instead of the sella turcica.

Structures from the Pharyngeal Portion of Rathke's Pouch (Hypophysis Pharyngei).—The pharyngeal portion does not atrophy, but gives rise to a structure called the pharyngeal hypophysis, which is situated in the middle line near the junction of the nasal septum and the roof of the pharynx, as is illustrated in Fig. 1. Lewis states that "the size of the pharyngeal hypophysis varies with age. It enlarges until middle life, when it becomes stationary and remains of the same size. In the embryo it measures three millimeters in length, in the newborn four millimeters, and in the adult five millimeters. In width it varies from one half to one millimeter. The pharyngeal hypophysis may have the form of a cord, which, especially in the embryo and newborn, may be irregular, being constricted at different points. It may have the shape of the letter S. There is no capsule in the embryo and newborn, but in the adult the connective tissue surrounding it is thicker and condensed to what might be called a capsule. The alveoli which are found in children are small and round or oval in form. Some of these in adults contain colloid. The tissue presents all the histologic features of the anterior lobe of the hypophysis occupying the sella turcica. The pharyngeal hypophysis is to be regarded as an actively functioning gland, rather than a rudimentary or involuting one."

Pende(*b*), on the other hand, is of the opinion that the tissue of the pharyngeal hypophysis is less highly differentiated than that of the hypophysis cerebri, and that it does not react in the same way experimentally. Further information regarding the pharyngeal hypophysis may be obtained from Bryant's paper.

Lobus Posterior.—The posterior lobe of the hypophysis is formed as a differentiation of the infundibular process of the hypothalamus and presents few developmental anomalies.

Growth and Development of Various Parts.—The growth phenomena of the hypophysis are interesting and suggestive, but unfortunately no statistics are available for man. In white rats Hatai finds that a sex difference appears in animals weighing fifty grams or more; that is to say, at precisely the same stage of development as in the case of the suprarenals. Jackson has found, likewise in the white rat, that after birth the anterior lobe increases and the posterior lobe decreases relatively in size. The relatively larger hypophysis in females he considers due to the larger anterior lobe. "In young rats, held at maintenance of constant body weight, the pars anterior is somewhat reduced, the intermedia and nervosa being correspondingly larger" (Jackson). The pars intermedia and posterior lobe resemble, therefore, the suprarenals and the

parathyroids in possessing a high growth energy. In congenital hypoplasia the anterior lobe is most affected.

We have no data for man on the time of maturity of the hypophysis. Lewis(*c*) has found that in pig fetuses between 125 and 175 millimeters in length "the secretion of the pars intermedia becomes as active as that of the adult gland." At birth the fetuses measure about 280 millimeters, and Lewis estimates that fetuses of 125 millimeters are "about nine and one half or ten weeks old from conception." As yet, we have no information relative to the anatomical changes coincident with the appearance of secretory activity in mammals.

Early Endocrin Function of the Hypophysis.—Smith's(*b*) observations on the anterior lobe of the hypophysis in young tadpoles have shown that, in these very early stages, this part of the hypophysis supplies a substance or substances having a specific action on growth and pigmentation. The fact that the secretions are thrown out before acidophilic and basophilic granules and other evidences of cell differentiation make their appearance, supports the conclusion (in the parathyroid section) that the optically homogeneous ground substance is the formative agent, and that the absence of visible secretion antecedents means but little. And furthermore, since we have no reason to believe that the adult hypophysis produces a substance which plays a part in pigment formation, we must conclude that its production, like that of so many other products of the endocrin organs, is restricted to very young animals. This brings up the point that we must not expect the extracts of the ductless glands of adult animals, when used in feeding experiments, invariably to possess the same physiologically active substances as those of young animals.

Comparative Anatomy

The hypophysis is a very ancient organ, which is represented in all classes of vertebrates. In the myxinoidea it discharges directly into the pharynx. In attempting to establish homologies in the vertebrate scale, Wörderman's work may be used as a guide. It is possible that we may be dealing with a succession of glandular organs, or of the responses of fundamentally similar organs to very different conditions. Certain it is that the size of the hypophyseal complex, relative to the brain as a whole, decreases very noticeably as we pass upward in the phylogenetic series. From a practical point of view, in mammals there are two chief variables, the extension of the cavity of the third ventricle into the posterior lobe, and the investment of the posterior lobe by the pars intermedia.

In man and most other mammals the posterior lobe is solid, but in the cat the pars nervosa is hollow and communicates freely through the infundibulum with the ventricle. For experimental purposes it is possible

to select animals exhibiting many stages in the closure of this connection.

The pars intermedia surrounds the pars nervosa to a variable extent—almost completely in the cat and scarcely at all in the sheep. In man and several other animals the pars intermedia "is most abundant around the

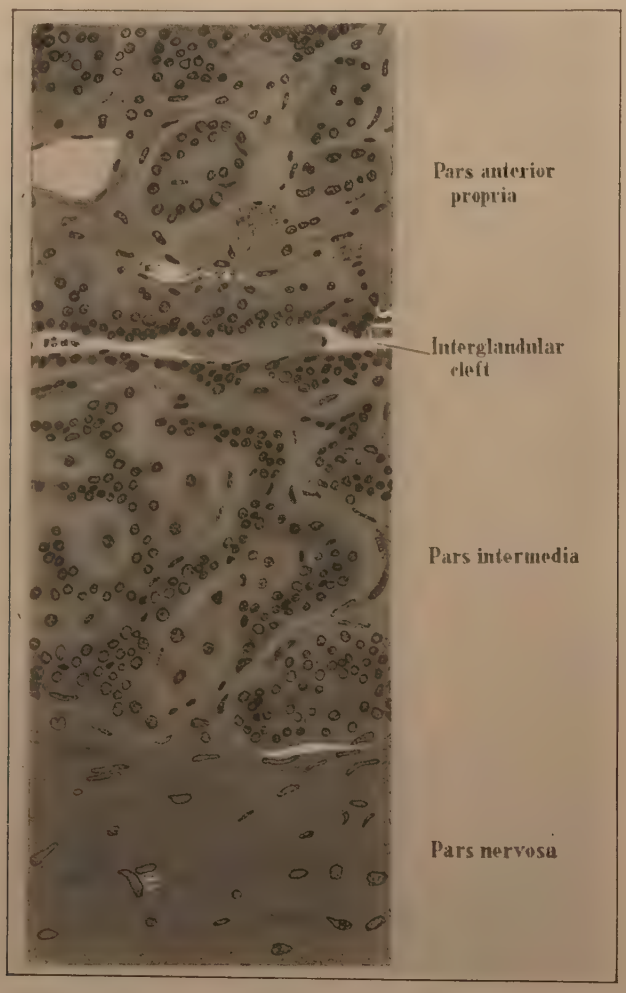


Fig. 4. Section through a sheep's hypophysis (magnification 400).

neck of the posterior lobe and spreads over and onto the adjacent surface of the brain" (Lewis). It is questionable, however, whether this is really pars intermedia or pars tuberalis. In position the tissue corresponds to the pars tuberalis which has recently been described in many representative vertebrates as a distinct and separate division of the hypophysis; but, according to Atwell, the pars tuberalis in the rabbit is developed from

two anlagen quite independent of the pouch of Rathke, so that for the present the question of the nature of this extension of anterior lobe tissue, in the human hypophysis, remains open.

Histology

The general appearance of the three main divisions of the hypophysis, as seen in a section passing from the anterior lobe proper through the pars intermedia into the posterior lobe, is illustrated in Fig. 4.

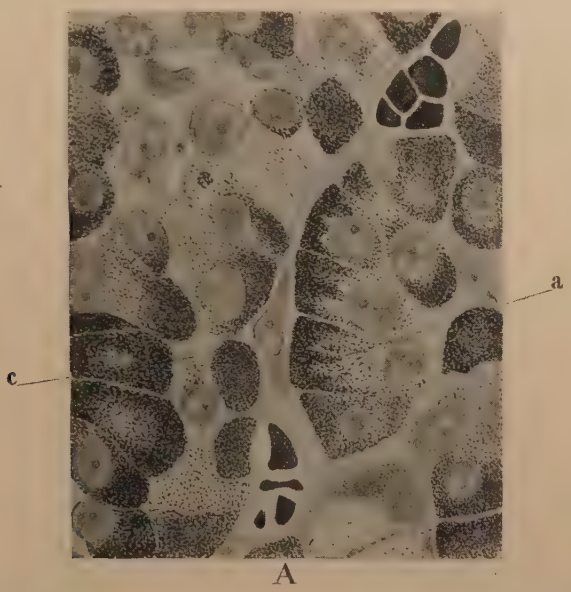


Fig. 5. Pars anterior of guinea pig's hypophysis fixed in Altman's fluid and stained with fuchsin and methyl green. (a) Acidophil cells, (b) basophil cells and (c) chief cells (magnification 1500). Area containing chiefly acidophil cells. Note in some cells the heaping up of granules in the pole of the cell next the blood vessels in the interstitial tissue, and that the chief cells (c) are often some distance removed from the blood vessels.

Pars Anterior Propria.—The pars anterior propria consists, for the most part, of epithelial cells arranged in clusters and columns separated by a small amount of connective tissue. Sometimes acinus-like structures with definite lumina are to be seen (Fig. 4). The clumping of the cells is less apparent in lower mammals than in man.

Cells Types.—There is but little uniformity in the classifications of the different cell types which have been proposed. The cells are usually divided into chromophil cells, which stain deeply, and chromophobe cells, which remain clear. In the chromophil cells it is customary to recognize two groups, those with basophilic cytoplasm, and those containing acido-

philic granules. The chromophobe, or clear cells, are also called chief, or principal cells and reserve cells (Addison(*a*)). According to Tilney(*a*), they are in reality faintly basophilic. We have then three cell types; (a) acidophil, (b) basophil and (c) chief cells. It is easy, however, to find apparent transitions between them. The basophil and acidophil varieties are usually considered to be descendents or differentiations of the chief cells, but their genetic and functional relations to each other are not at all well understood. At present we do not know whether both of them have definite and specific functions to perform, or whether they represent stages in a single type of activity. The chief cells are distributed fairly

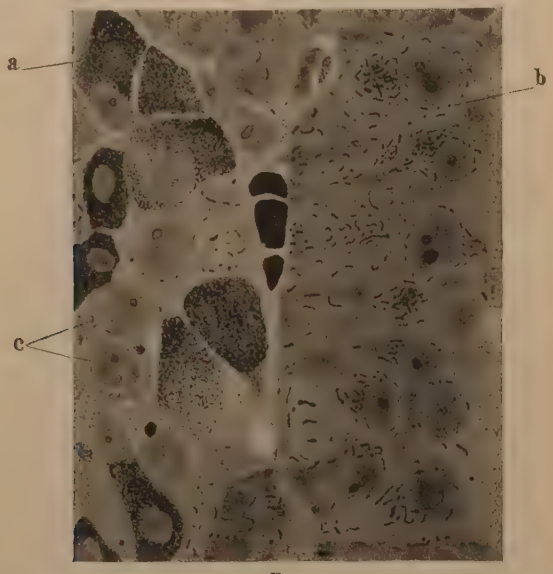


Fig. 6. The same hypophysis area containing for the most part basophil cells.

evenly throughout the anterior lobe, while the acidophil cells are usually most abundant in its posterior part. The chief cells (c) are often surrounded by the basophil (b) and acidophil (a) varieties, so that the latter are brought into close association with the capillaries (Fig. 6).

Cytology.—The structure of the cells has not been very carefully worked out. It is not clear whether they possess a definite secretory polarity in which the capillaries take the place of the usual gland ducts; but the heaping up of granules near the blood vessels, illustrated in Fig. 5, would seem to indicate that this may be the case. From birth onward most of the cells contain a small number of fat droplets which stain with Sudan III and blacken with osmic acid. As in other tissues, the fat increases with old age. The nuclei of the different cells are similar, except perhaps for slight differences in size. The mitochondria are well known

and resemble those occurring in other glands. They may be distinguished from the other granules by their rod-like and filamentous shape. In lower forms, Gemelli has described a reticular apparatus, comparable to the Golgi apparatus of nerve cells. In his preparations it occurs in the form of a loose network with large meshes blackened with silver. Addison has confirmed and greatly extended Gemelli's results in mammals. The basophilic cytoplasm is often apparently homogeneous, but large discrete granules staining intensely with basic dyes are not uncommon. The acidophil, or oxyphil granules are very conspicuous, and are thought by Benda to represent the true secretory antecedents of the gland.

Effects of Various Conditions on Hypophyseal Cells.—(1) *Pregnancy.*—The chief cells undergo remarkable changes during pregnancy. Erdheim and Stumme have found that they increase greatly in number, becoming even more abundant than the acidophil cells. They increase also in size and their cytoplasm becomes faintly acidophilic. After the termination of pregnancy they resume their old properties, but the increase in number is never entirely lost. The process is repeated at the next pregnancy.

(2) *Castration.*—Kohn observed an increase in the number and size of the chief cells three years after castration. Addison(*b*) has made a careful study of the effect of castration in the rat. He found that "the basophils increase in size and number. The largest begin to become vacuolated at two months after operation. During succeeding months the number of vacuolated cells increases; the largest become ringshaped, with cytoplasm and nucleus at the periphery, and the central part made of the colloid containing vacuole. The acidophils are not much affected at first, except for a slight diminution in average diameter. Gradually some of them show a diminished number of granules and lessened stainability. At seven months after castration the number of distinctly stained acidophils is decidedly reduced. Some of the reserve cells in the first months after castration appear to become basophil cells. In the later months some of the acidophils appear to gradually dedifferentiate into reserve cells."

Addison did not observe the great increase in acidophil cells which is usually recorded.

(3) *Endocrin Gland Extirpation and Administration.*—According to Kojima's(*b*) observations, total thyroidectomy causes in the rat a deposition of hyaline substance in the pars anterior. Addition of thyroid, anterior lobe, and epinephrin to the food all cause an increase in the number of acidophil cells. Iodids, on the other hand, bring about a reduction in both the acidophils and basophils. Parathyroidectomy exercises a similar, though less apparent effect. Whatever the relationships of these different cells in the anterior lobe, a delicate balance is maintained through the growth and differentiation of the chief cells.

(4) *Hibernation.*—The hypophysis undergoes marked alterations in

structure in different physiological states. In hibernation, for example, in the woodchuck, Cushing and Goetsch(*b*), among others, have found that the gland not only diminishes in size, but the cells of the pars anterior, in some animals at least, lose their characteristic staining reactions to acid and basic dyes. At the end of the dormant period the gland swells, and as the cells enlarge they again acquire their differential affinity for acid, basic, and neutral stains, and at the same time karyokinetic figures may appear." Jackson thinks that these changes are brought about by the inanition during the long period of fasting. This interpretation would seem to indicate that the hypophyseal changes are not caused, since hibernation cannot be induced through inanition. Gley's statement that the cells of the hypophysis exhibit a chromaffin reaction is difficult to verify.

Pars Intermedia.—In the pars intermedia we find a few indeterminate cells which have been variously called ependymal, neuroglial, and supportive. They may be stained specifically by the Golgi method, and are thought to have migrated into the pars intermedia from the neighboring posterior lobe.

Cytology.—The glandular cells proper are arranged in small clumps and clusters, separated by a connective tissue framework containing blood vessels, lymphatics, and possibly also nerves. These cells of the pars intermedia are quite different in structure from those found in the anterior lobe. They are somewhat smaller and, in place of the conspicuous eosinophil granules, they often contain a fine neutrophilic granulation (Schafer(*d*)). It has been claimed that they contain glycogen. Mitochondria are to be seen, but a reticular apparatus has thus for not been clearly described. There is but little evidence of secretory polarity. Definite intracellular secretion antecedents have recently been described by Lewis and Maurer. That the pars intermedia is much less vascular than the anterior lobe may be seen by reference to Fig 3.

Colloid of the Hypophysis, Its Occurrence, Nature and Function.—The cells bordering the interglandular cleft are columnar in shape (Fig. 7) and may be even ciliated. In the deeper portions they show a tendency to be arranged in small vesicles bearing a certain superficial resemblance to those of the thyroid gland. The vesicles often contain a hyaline or colloid material which stains intensely with eosin; associated with this is a lesser quantity of basophilic granular substance, suggestive also of the thyroid. Biedl(*b*) asserts that this colloid material has been identified with that of the thyroid gland, citing the discovery of iodin in the hypophysis in support of his contention. Schafer, on the other hand, accepts the evidence advanced by Simpson and Hunter, that the colloid material is devoid of iodin and quite different from that of the thyroid gland. According to Schafer, "this 'colloid' or 'hyalin' substance appears to be produced by a transformation of the protoplasm of some of the cells of the pars intermedia, for the globules not infrequently contain a

nucleus. They vary in size, some being smaller than the epithelium cells, others many times larger; they are most numerous in the part of the pars intermedia which merges into the pars nervosa."

In the sheep's hypophysis (Fig. 7) the interglandular cleft, between the pars anterior propria and the pars intermedia, contains a mass of colloid which is very definitely stratified, suggestive perhaps, of alternating periods of rest and activity. The desquamated cells in the lumen call to mind like conditions in the thyroid gland.

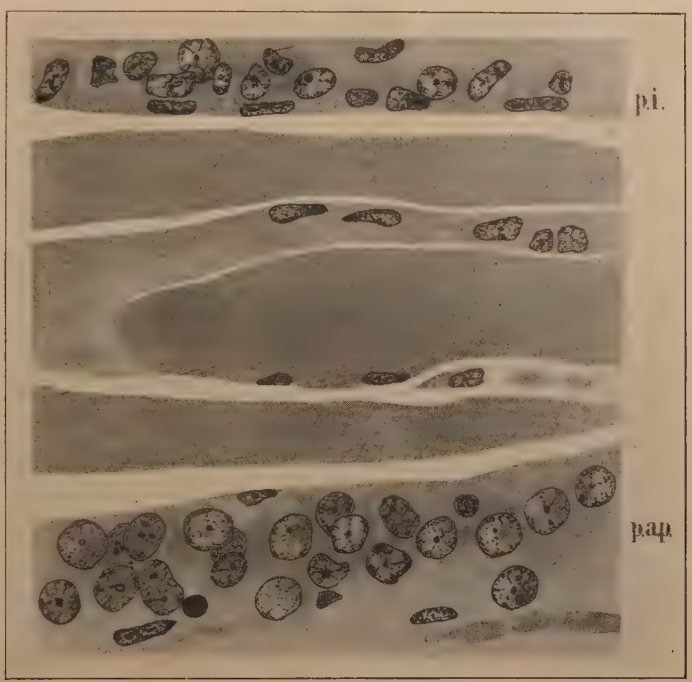


Fig. 7. Pars intermedia (p. i.) and pars anterior propria (p. a. p.) of sheep's hypophysis showing lamination of colloid substance (magnification 800).

Opinions differ concerning the interpretation which we should place upon this colloidal material. Some think that it is a degenerative product, others consider it to be a remnant of a hypothetical external secretion. By far the majority of recent investigators, however, look upon it as a true internal secretion. The increase in amount following thyroidectomy and on removal of the pancreas supports this conclusion. The mode of discharge of the colloid has been much debated. Biedl writes that "the presence of the colloid substance between the cells, in the vesicles, and in the lumen of the capillaries, is regarded as proof of its excretion by way of the blood stream." Herring has reported the observation of all stages in the passage of the material through the posterior lobe into the cavity of the third ventricle. Atwell and Marnus point out that the material, as

found in the posterior lobe, has quite a different staining reaction from the contents of the acini of the pars tuberalis in the ox.

There is a very marked increase in size of the hypophysis, particularly of the pars intermedia following removal of the thyroid, as well as after castration in young animals.

Pars Nervosa.—The pars nervosa consists chiefly of neuroglia fibers with a few scattered neuroglia cells (Fig. 4). True nerve cells are absent. Both blood vessels and nerve fibers are of rare occurrence. Dark greenish yellow pigment is often found free in the interstices between the fibers and in the scattered neuroglia cells, as well as in the ependymal cells lining the ventricular cavity. The distribution of this pigment has been studied in detail by Kohn(*a*). Quite frequently the cells of the pars intermedia tend to migrate into the adjacent portions of the posterior lobe. Globules of colloid occur in the meshwork of neuroglia fibers, which are formed in the pars intermedia, and are perhaps being discharged into the third ventricle, as Herring believes. There is no anatomical evidence of a secretion being formed by the posterior lobe itself, or of the presence in it of "at least two specific autacoids," as claimed by Schafer on physiological grounds.

Cushing and Goetsch(*a*) claim to have shown that the active principle of the posterior lobe is discharged into the cerebrospinal fluid. This, however, is contradicted by Carlson and Martin, whose criticisms appear to be well taken. Until the matter is finally settled, however, the possibility should be always entertained that the material passes in both directions, into the blood vessels and into the ventricular fluid, and, furthermore, there is no reason to doubt that other physiologically active substances which have escaped notice are liberated.

Physiology and Experimental Pathology of the Hypophysis ..... *Dean Lewis*

Results of Extirpation of the Gland—Feeding Experiments—Whole Gland Feeding—Polyuria Associated with Lesions of the Hypophysis.

Physiology and Experimental Pathology of the Hypophysis

DEAN LEWIS

CHICAGO

Marie in 1886 called attention to the relation between acromegaly and the hypophysis. Many of the tumors of the hypophysis in the earlier cases of acromegaly were regarded as sarcomas and it was believed that the symptom-complex was due to a destructive lesion of the gland. Later studies have shown, however, that acromegaly is always associated with hyperplasia or adenoma of the eosinophile cells of the anterior lobe of the hypophysis and that the early tumors which were regarded as sarcomas were really adenomas of the anterior lobe.

The clinical and pathological investigations of acromegaly and the hypophysis stimulated experimental work upon the gland, much of which was at first undertaken with the view of producing some of the changes which were observed clinically when the gland was diseased. These studies have been carried on rather intensively for a number of years by several different investigators. There are many questions relating to the hypophysis which are still unsettled, conflicting evidence being found, but a number of facts upon which conclusions may be based have been determined.

Results of Extirpation of the Gland—Partial and Complete.—Horsley (1886) was the first to attempt extirpation of the hypophysis, in order to compare the effects of removal of this gland with those of the removal of the thyroid. His work, like that of Dastro (1889) and Gley (1891), was not at all satisfactory for practically all of the animals died shortly after the operation. Marie and Marinesco regarded acromegaly as due to lessened function of the hypophysis and Marinesco attempted in 1892 to reproduce the symptom-complex experimentally. He operated upon a number of different animals in different ways, but his results were not at all conclusive because it was difficult to determine in many of these early studies whether the symptoms were due entirely to removal of the

[1] Marie P—— Sur deux cas d'acromégalie, hypertrophie singulière non congénitale des extrémités superieure inferieures et cephaliques—Rev. de Méd., 1886, p. 298.

gland. The technic was not refined and many of the results were undoubtedly due to infections or injuries of the brain. As the operations were often done through a small incision it was correspondingly difficult to determine whether the gland was partially or completely removed.

Paulesco(*a*) (1906) employed the lateral or temporal route for exposure of the hypophysis. In this operation the gland may be exposed so well that one or the other lobe may be removed, or the stalk divided as desired. It should be remembered, however, that even after total hypophysectomy the portion of the pars intermedia, which is reflected onto the floor of the third ventricle—the so-called pars tuberalis—is left behind.

Paulesco attempted total hypophysectomy upon 22 dogs and cats. Ten of the animals died within 48 hours following the operation. No adequate cause of death was found at autopsy in these cases for there was no evidence of infection. The investigator concluded, therefore, that the death of these animals must have been caused by the loss of hypophyseal secretion. In 14 animals the hypophysectomy was not complete, for at the autopsy remnants of the hypophysis of varying sizes were found. If the pieces of the hypophysis which had been left were small the animal survived but a few days (3-10); but those animals in which larger pieces had been left lived some time, one as long as 395 days.

Even almost total destruction or removal of the hypophysis seemed not to give rise to any particular group of symptoms or trophic disturbances.

In seven animals a total destruction of the cortical substance of the anterior lobe was caused by a thermocautery. These animals died shortly after the operation; the destruction of the cortical portion of the anterior lobe is the equivalent of total hypophysectomy as far as the life of the animal is concerned.

In three animals partial destruction of the anterior lobe was performed. These animals lived respectively 23, 36 and 132 days without developing any noticeable symptoms.

The posterior lobe was removed in five animals, one of which lived two years after the operation and then died of some intercurrent disease. Removal of the posterior lobe seemed to have no especial effect upon the animal, but separation of the stalk was followed by death, stalk separation being the equivalent of total hypophysectomy.

It is a little difficult to reconcile these last findings for posterior lobe removal would seem to be almost the equivalent of stalk separation. In stalk separation the operative procedure is carried up near the floor of the third ventricle, but opening of the third ventricle or injury of the same, the experiment having been performed as control, does not have the effect ascribed by Paulesco to stalk separation. It is quite possible that in stalk separation some of the vessels supplying the anterior lobe are injured

and that the results following stalk separation should be ascribed to loss of anterior lobe function rather than to separation of the stalk.

Paulesco came to the conclusion as a result of his experimental work that the hypophysis is essential to life; and that total hypophysectomy is followed by death within a few hours. According to him the cortical part of the anterior lobe is the part of the gland which is indispensable to life.

Those animals which survived the operation in which small portions of the anterior lobe had been left behind apparently did not develop any train of symptoms which might be likened to dystrophia adiposogenitalis in man, for even small portions of the anterior lobe seem to be able to supply enough secretion to maintain the normal metabolic processes of the body.

In 1909 Cushing and his associates published their first papers dealing with the results of complete and partial hypophysectomies. Young animals apparently survived total hypophysectomy longer than did older ones. Total removal of the hypophysis was followed after some days or at the latest after some weeks by a peculiar train of symptoms—cachexia hypophyseopriva—which terminated fatally.

Partial removal of the anterior lobe is according to Cushing not incompatible with life. In some cases, however, partial removal is followed by a peculiar train of symptoms. The animals become fat and apathetic and lose sexual power, the hair falls out and the genital organs undergo decided atrophic changes. There may be a transitory glycosuria and in some instances there develops after the operation a marked polyuria which is transitory. Polyuria will be discussed more at length when discussing the effects of injections of hypophyseal extracts. The symptom-complex which follows partial removal of the anterior lobe is quite comparable to Fröhlich's syndrome—dystrophia adiposogenitalis—as it appears in man, due usually to interference with hypophyseal function from tumors developing in the gland proper, or pressure of tumors situated in the neighborhood.

Aschner in 1909 published a paper upon the results of removal of the hypophysis in which the operation was performed through the buccal route. He believed that some of the results of total hypophysectomy which had been reported by Paulesco, Cushing and Biedl were due to injury of the brain following the manipulations which were necessary to expose the hypophysis by the temporal route.

Some of Aschner's animals died within 8 days, as a result, he believes, of removal of too much of the infundibulum. In the adult animals that survived no special symptoms developed. The young animals, however, developed a definite train of symptoms. They took on fat rapidly, became apathetic and did not bark, the genitalia did not develop or become

atrophic, the hair fell out, the epiphyseal cartilages persisted, spermatogenesis ceased in the male and regressive changes occurred in the ovarian follicles in the female. These are much the same changes described by Cushing in the animals in which partial removal of the anterior lobe had been performed—corresponding to the changes of dystrophia adiposogenitalis as observed in man.

There is no doubt that the hypophysis can be removed by the buccal route with less injury to the brain than through the temporal route, but infection occurs more frequently when the buccal route is employed. It is surprising, however, how infrequently infections occur even when this operation is employed. Aschner is probably correct when he states that some of the symptoms ascribed to hypophysectomy by the temporal route may be due to injury of the brain, but he himself is subject to criticism, for he has not controlled sufficiently his operations by histological studies to state with certainty whether or not a total hypophysectomy was achieved. It is quite possible that in many of the adult animals operated upon by him which developed no symptoms after a supposedly complete hypophysectomy, a remnant of the anterior lobe remained.

Experimental removal of the entire hypophysis indicates that the organ is essential to life. Removal of the anterior lobe is the equivalent of total hypophysectomy. The anterior lobe therefore forms the secretion which is indispensable.

Partial removal or destruction of the anterior lobe in young animals is followed by a peculiar train of symptoms—taking on of fat, genital atrophy, falling of the hair, temporary polyuria and glycosuria, and skeletal changes, which are quite comparable to the changes of dystrophia adiposogenitalis or Fröhlich's syndrome as observed in man.

Removal of the posterior lobe, in which is included the greater part of the pars intermedia—has no early or late results.

Stalk separation apparently is fatal. It is rather difficult to reconcile this with the fact that removal of the posterior lobe has no effect. It is possible that the operative procedures necessitated in stalk separation or division injure vessels supplying the anterior lobe and that the fatal issue in such cases is determined by anterior lobe changes rather than by the stalk separation alone.

It has been suggested that many of the changes associated with dystrophia adiposogenitalis are due to interference with or alteration of posterior lobe secretion—which means pars intermedia secretion. There seems to be no experimental evidence to support this claim.

Feeding Experiments.—As pathological evidence accumulated which indicated that acromegaly is dependent upon hypersecretion of the anterior lobe of the hypophysis, feeding experiments were undertaken with the

hope of producing the disease or at least of causing some skeletal or metabolic changes which might be comparable to those observed in this disease. Several metabolic studies have been made upon animals being fed hypophyses.

Thompson and Johnson fed dogs the whole dried gland of the sheep, horse and calf. Animals so fed lost weight and excreted excessive amounts of nitrogen and phosphorus. The results were apparently more marked when the glands of young animals were fed. Oswald gave dogs 2 to 3 gm. daily of dried hypophysis (whether whole gland or portion of the same not mentioned) but could not detect any change in the elimination of nitrogen or P_2O_5.

Malcolm fed dogs daily 2 to 3 gm. of dried anterior lobe for five days. A slight nitrogen retention and a slightly increased P_2O_5 and Ca output were noticed in them. After feeding posterior lobe (10 gm.) there was noticed a slightly increased output of P_2O_5 and a markedly increased output of Ca. When fresh whole glands were fed there was scarcely any change in the Ca or Mg output.

Franchini injected rabbits intravenously daily with an amount of extract equivalent to one whole hypophysis. These injections were followed by an increased excretion of Ca, Mg and P_2O_5 in both the urine and feces. The loss in P_2O_5 was less marked than that of Ca and Mg. These animals lost weight and finally died. The injections did not have much effect upon some of the animals; while others developed marked dyspnea, vomiting and diarrhea. In some of the animals intestinal ulcerations were found at autopsy. No definite conclusions can be drawn from these experiments as to the effects of hypophyseal feeding upon metabolism, because the findings are so indefinite and because of difficulties of control.

Few of the early feeding experiments were satisfactory because no attempts were made to feed the parts of the gland separately. When the extract has been administered subcutaneously or intravenously (Cerletti, Franchini, Delille, Caselli) marked constitutional disturbances such as vomiting and diarrhea, accompanied by intestinal ulceration have been observed.

The possibility that these constitutional symptoms are not due entirely to the extract cannot be eliminated and therefore it is difficult to draw conclusions regarding the actual effects of hypophyseal extracts upon body growth and metabolism. Cerletti and Franchini report loss of weight and delayed bone development. In their experiments the entire gland was used but the injections were continued for but a few days. Caselli injected young dogs and rabbits with glycerin extracts. No effect upon growth was noted. Delille reports increased deposits of fat in rabbits after injecting them for a period of fourteen months with extracts of the whole gland.

Landri fed rats the hypophysis exclusively for two months, the con-

trols being given meat. He believed that the animals fed the anterior lobe gained more weight than the controls but the figures indicate that the gains were so slight that they could scarcely be regarded as significant. The controls gained during the two months, on an average, 10 gm.; those fed on the posterior lobe 7 gm. and those fed on the anterior lobe 12 gm. Variations of this amount may occur in any series of feeding experiments continued over this period.

In Schaefer's feeding experiments, four young rats were fed small amounts of the dried anterior lobe mixed with bread and milk, while the controls were fed powdered testicle or ovary with bread and milk. The amounts consumed by each group of rats were accurately determined. The experiments were carried through a period of three months. At the beginning, the average weight of the group fed upon the hypophysis was 44.25 gm.; that of the controls was the same. At the end of the experiment the average weight of the rats fed on the hypophysis was 150 gm., that of the controls 131 gm. During the first six weeks of this feeding experiment litle difference between the two groups was noted, but during the last six weeks those fed on the hypophysis made the more rapid gain.

Lewis and Miller in 1912 undertook feeding experiments with the view of observing several series of animals with controls. Young rats were selected for the experiments and each one was placed in an individual cage. Fresh ox hypophyses were used for feeding; the anterior and posterior lobes were separated, chopped up and dried in a blower at a temperature of approximately 100° F. The dried glands were then powdered and a weighed amount added to powdered cracker, the mixture being pressed into a tablet. It was then determined how much of this food each rat would consume daily.

There were some individual differences but it was possible with reasonable accuracy to determine the daily ration. Cracker tablets of the desired weight were prepared and to each was added a weighed amount of the hypophysis or, in case of the controls, of meat. Each animal received the same amount daily. Occasionally a rat might not eat the whole tablet, but a note was made of this. The ration was with rare exceptions consumed daily. The rats gained in weight and appeared healthy, indicating that they were properly fed. Three series of animals were fed in this way for about three months. At the end of this time they were killed and examined. Radiograms were taken to determine whether or not there were any bony changes.

The first series consisted of nine rats. Three received daily 2 gm. of dried anterior lobe; three the same amount of posterior lobe, and the three controls the same amount of meat.

The second series consisted of 8 rats. Four were fed 4 gm. of the

anterior lobe and the other 4 used as controls were fed the same amount of dried meat. These animals were fed for ninety days.

The third series consisted of nine rats which were divided into three groups. One group was fed daily 3 gm. of beef; another the same amount of posterior lobe and the remaining group was fed dried thymus.

It is interesting to note that animals consuming the same amount of food daily and apparently enjoying equally good health should vary so much in weight gaining. The minimum gain in weight of the controls in Series I was 30.6 gm., the maximum 44.4 gm. In Series II the minimum gain in weight of the control rats was 32 gm., the maximum 38.5 gm. In Series III the rats were but two-thirds grown and not so well suited to the experiment. One of the controls and one fed on the posterior lobe lost 5 gm.

FEEDING EXPERIMENTS—LEWIS AND MILLER

Number of Animals	Food Daily, Gm.	Average Weight at Beginning, Gm.	Average Weight at Termination, Gm.	Change in Weight, Gm.	Period of Feeding Days.
	SERIES I				
3	Dried beef, 0.2	52.2	91.8	38.6	78
3	Dried anterior lobe, 0.2	54.2	92.3	37.9	78
3	Dried posterior lobe, 0.2	58.1	102.6	44.5	78
	SERIES II				
4	Dried beef, 0.4	58	95.2	37.2	90
4	Dried anterior lobe, 0.4	66.6	107.3	40.7	90
	SERIES III				
4	Dried beef, 0.3	131.6	144.3	12.6	67
4	Dried posterior lobe, 0.3	115.3	121.5	6.2	67
4	Dried thymus, 0.3	118.6	135.3	16.7	67

It will be seen by the table that in the first series the controls and the rats fed on the anterior lobe gained practically the same amount, while the animals fed on the posterior lobe gained on an average 6 gm. each, more than the controls. Individually one of those fed on the posterior lobe gained less than one of the controls; the other two gained more than the controls and each animal fed on the posterior lobe gained more than those fed on the anterior lobe. In series III the animals receiving the posterior lobe gained less than the controls and much less than those animals being fed the thymus. In series I animals receiving the anterior lobe gained slightly less than the controls, while in series II they gained somewhat more than the controls.

Radiographs of these animals failed to reveal any changes in the skeleton.

Lewis and Miller conclude that, at least in their series, neither anterior nor posterior lobes of the hypophysis when given by mouth have any effect upon the growth or weight of the animals. The amounts administered were large enough to give results as they would be equivalent to 230 gm. daily for the average man. On the other hand, the amounts were not large enough to have a deleterious effect, for the animals so fed gained in weight as did the controls. Doubling the amount of the anterior lobe did not modify the results. It must be admitted, however, that this does not prove that increased or altered hypophyseal secretion may not modify growth. In the feeding experiments digestive fluids may destroy the active principles and besides, the administration of these extracts by mouth is scarcely comparable to the continuous secretion from the gland *in situ*.

Goetsch(*a*) has obtained positive results from feeding experiments. His conclusions are as follows:

Whole Gland Feeding.—The dried powdered pituitary extract derived from both the anterior and posterior lobes of the gland when fed to young rats in excessive doses (0.1 gm. daily), causes failure to gain in weight, loss of appetite, increased peristalsis, mild enteritis, and certain nervous manifestations such as muscular tremors and weakness of the hind limbs. The latter symptoms are undoubtedly due to the posterior lobe element in the whole gland extract, for they are similarly produced by using posterior lobe, but not by using anterior lobe extract. Even when the whole gland is fed over a short period of time, from 25 to 40 days, it causes a more rapid growth and development and gain in weight, larger nipples in the female, and a coarser, drier, harsher growth of hair than are seen in either control animals or after administration of ovarian (corpus luteum) extract in equivalent dosage.

In comparison with the development in control animals, the ovaries, tubes and cornua of the uterus of animals fed with whole gland extract were larger, more vascular and edematous in appearance, indicating increased development and activity. Even at the early age of two and two-fifths months (from one to two months before normal sexual maturity) the ovary was matured and showed active ovulation and Graafian-follicle formation, relatively few primordial follicles and some increase in the amount of interstitial tissue. This rather striking appearance in so young an animal gives one the impression that an early ovarian maturity was produced by the feeding of pituitary extract. The fimbriated end of the tube was more branched and the lining columnar cells more ciliated, an indication of greater activity. There was marked hyperplasia of the uterine mucosa, the lining cells of which were more uniformly ciliated and active and there was abundant gland formation in the endometrium.

The appearance presented by the latter strikingly resembled in microscopic appearance the hyperplastic endometrium of early pregnancy. There was generally increased vascularity produced in the whole sexual system. The overdevelopment was apparent even in the muscle coats of the uterus, which were considerably thickened and also more vascular. A somewhat similar change was produced by the feeding of corpus luteum to the female.

In the male subjects the testes showed a considerably earlier growth and development; they were completely and permanently descended at an earlier age, and their gross weight was greater than in a control animal. This is evidenced by extremely active spermatogenesis, with formation of spermatozoa, by a moderate increase in the amount of interstitial tissue, at a time when the control animal was sexually still very immature. All these developmental, structural and functional changes in the sex glands of both the male and female, produced by the feeding of pituitary extract, show an extremely selective and almost specific action of the latter upon the genital system.

Anterior Lobe Feeding.—The feeding of pituitary anterior lobe extract caused increased weight and greater and more vigorous body growth and development over the control. There was similarly an earlier and more active genital development. The fur was harsher and thicker. Loss of weight, enteritis, and nervous manifestations were not observed as in the beginning of whole gland feeding. As compared with the control, the animal fed with anterior lobe for only 40 days showed an early descent of the testes, which were also larger, more vascular and heavier, not absolutely but in proportion to the body weight. The testis was mature at least as early as two and one-half months, after 40 days of anterior lobe feeding. The period of complete sexual development was shortened by at least one month, or about one-third of its normal time. Histologically, the testis at this age was mature; it showed an abnormally early and active karyokinesis, more active in fact than was seen in the testis of a supposedly normal rat at the age of from three to four months. The testis of the control at this same age was quite immature. The interstitial cells did not seem to have increased in number proportionately to the increase in spermatogenic cells and spermatozoa. The epididymis contained more spermatozoa and had a more active-looking structure. The prostate gland, seminal vesicle and vas deferens showed a correspondingly early and increased development and activity. These changes produced by the feeding of anterior lobe indicate that the latter supplies the active principle in the whole gland responsible for the changes reported above, following the feeding of whole gland extract.

After prolonged feeding of anterior lobe extract, over a period of eight or nine months, the sexual instincts were early awakened, along

with early maturity of the sex glands. As a result of this a pair of rats after anterior lobe feeding over a number of months bred earlier and oftener, having two pregnancies in 7 months, as compared with none in the female of the control pair.[1] The effect of anterior lobe feeding lasted throughout the adult life of the animal. The control rat never reached the degree of development and activity shown by animals receiving the anterior lobe extract. For even at the age of 10 months, after eight and one-half months of anterior lobe feeding, the latter still showed a greater, more active and mature sexual development than the control.

The feeding of pituitary anterior lobe to parent rats exerted its stimulating influence upon the offspring in intra-uterine life and during lactation, and, when the experiment was carried further, and the feeding to the young continued after weaning, it had even greater stimulating effect upon growth, weight and development and caused earlier and more frequent breeding and an increased number of offspring in the litters. The stimulating effect upon the sex glands was greater the longer the influence of anterior lobe administration was exerted.

Posterior Lobe Feeding.—The extract of pituitary posterior lobe, even after prolonged administration, did not stimulate growth in general, nor the development of the sex glands, as did anterior lobe even after a very short period. Thus, for example, there was a very much less marked development of the sex glands after administration of posterior lobe for seven and one-half months, than after anterior lobe administration for two and one-half months. The posterior lobe element in the whole gland had an undoubted retarding influence upon the development of the sex glands, an effect very similar to that of ovarian extract upon the testes. This is shown in the relatively incomplete development of the testes, for example, after eight and one-half months of posterior lobe feeding. If given in too large a dose, the extract causes in the rats loss of weight, mild enteritis and increased intestinal peristalsis.[2]

It will be seen from the experiments dealing with hypophyseal feeding how the results differ and how complicated the problems are when an attempt is made to reconcile them with clinical observations. Acromegaly is due to an overactivity of the anterior lobe. As before mentioned it is probably due to overactivity of the eosinophile cells, but impotence in the male and amenorrhea in the female are often among the earliest symptoms; quite the contrary of the activity in the sexual organs resulting from feeding the anterior lobe as reported by Goetsch. Hypophyseal feeding has not been successful in cases of dystrophia adiposogenitalis, even in those cases in which the syndrome has developed as a result of failure of the

[1] The failure of a white rat to breed within this period obviously indicates that it or its mate was not normal. R. G. H.

[2] Several careful observers, using more adequate series, have failed to corroborate the results obtained by Goetsch on feeding hypophysis as herein reported. R. G. H.

hypophysis to go on to full development and in which there have been no evidences of tumor.

The rôle which the posterior lobe plays in causing some of the symptoms observed in acromegaly and dystrophia adiposogenitalis is not understood and physiological experiments have failed to throw light upon this question.

Polyuria Associated with Lesions of the Hypophysis.—Experimentally a marked polyuria may follow operative procedures upon the hypophysis. The exact nature of the lesions causing such polyuria is still under discussion.

Kahler in 1886 in analyzing 22 cases of diabetes insipidus found the lesion in seven of these about the infundibulum, the substantia perforata posterior and the corpora mammillaria.

In 1913 Lewis and Matthews reported 18 experiments relating to diabetes insipidus. The hypophysis was approached through the buccal-transpalatosphenoidal route.

The following may be cited as a typical example of polyuria following operative interference.

Experiment 10.—Dog weighing 4.5 kgm. was operated upon October 6, 1912, and killed October 12, 1912. The hypophysis was exposed and injured by a cautery. The animal passed on

October 6-7	2450	c.c. of urine,	sp. gr. 1.000
October 7-8	3900	c.c. of urine,	sp. gr. 1.000
October 8-9	900	c.c. of urine,	sp. gr. 1.007
October 9-10	300	c.c. of urine,	sp. gr. 1.012

In this case the anterior lobe of the hypophysis was injured. Eighteen animals were operated upon. Nine developed polyuria after the operation and nine did not. In an animal which developed the most marked polyuria, passing 5000 c.c. of urine during the first 24 hours, a large amount of pars intermedia was found in the specimen. The cells of this remnant took, however, a much heavier stain than normally.

In all of the nine specimens removed from animals which had marked polyuria, distinct remnants of pars intermedia which appeared to be in good condition were found. Remnants of pars intermedia were found in 4 animals which had no polyuria. In one of these there were distinct evidences of a marked inflammatory reaction about the pars intermedia and the animal presented general symptoms from the beginning, which undoubtedly would have abolished or modified a polyuria. In two other cases in this group the remnants of the pars intermedia were badly damaged, being surrounded by a fairly large blood clot. In one the remnant of pars intermedia was in good condition and it would have been judged from a histologic examination that the animal from which this specimen was removed might have had polyuria.

Total removal of the hypophysis was not apparently followed by polyuria, neither was injury of the anterior lobe alone.

Camus and Roussy(*b*) have come to the following interesting conclusions concerning the relation of the hypophysis to diabetes insipidus and glycosuria.

In a large number of hypophysectomies, partial or total, performed by them through the buccal-transpalatosphenoidal route, they observed marked polyuria. In the first two animals operated upon the polyuria was so great that the urine overflowed the 1 and 2 liter receptacles which had been placed beneath the cages.

They came to the conclusion as a result of their experimental work that the polyuria is not due to interference with hypophyseal function, for removal of the hypophysis (whether total or limited to one lobe) did not influence diuresis. A total hypophysectomy was performed upon two animals, one of which developed polyuria, and one did not. In the animal which developed the polyuria it was found that the base of the brain had been injured.

As a result of this observation they later began to injure the part of the floor of the third ventricle which borders upon the hypophysis with a heated needle, the hypophysis being carefully spared. They performed this experiment 5 times and in each instance produced a marked polyuria. No change was found in the hypophysis in any of these cases.

Another experiment performed upon two animals consisted of removal of the hypophysis. After this operation—total hypophysectomy—transitory polyuria was noted. At the second operation which was performed after a lapse of some time polyuria equalling in intensity or even more marked than the first developed. In both of these operations the base of the brain was injured, the first time unintentionally and the second time intentionally. In one animal the polyuria was extreme, lasting from October to May. In this animal glycosuria was noted for several hours after the puncture.

Camus and Roussy came to the conclusion that the lesion which determines whether or not a polyuria develops is in no way connected with the hypophysis. In five of their cases in which an intense polyuria developed the hypophysis was unaffected. Total hypophysectomy performed without injuring the base of the brain is not followed by polyuria. Previous removal of the hypophysis does not prevent the development of polyuria, if, during the second operation, the optopeduncular region is injured.

A superficial lesion of the base of the brain, often involving only the surface and produced involuntarily in the removal of the pituitary body, is followed by polyuria.

The optopeduncular region marks the zone within which a lesion

causes polyuria. This lies at the level of the gray substance of the tuber cinereum near the infundibulum. A lesion in front of this zone at the level of the chiasm or back of it at the level of the protuberance is not followed by polyuria.

Hanchett has made some interesting observations in this connection. He attempted to produce polyuria in animals. Electrical stimulation and heat did not avail. Polyuria could, however, be produced almost invariably by removing the floor of the sella and allowing the hypophysis to prolapse into the pharynx. This operation with its attendant pull upon the infundibulum gave rise more constantly to polyuria than any other type of operation.

A peculiar effect of spinal puncture upon diabetes insipidus has been observed by Herrick and Cammidge. The patient observed by Herrick reacted rather violently after a spinal puncture, but the urinary output rapidly decreased within twenty-four hours, with a marked increase in specific gravity. The reduced urinary output continued for some three months when the polyuria again developed. Cammidge's patient, suffering with diabetes insipidus, has apparently remained cured since the spinal puncture. In neither of these cases could a hypophyseal tumor be found.

Clinical evidence indicating that diabetes insipidus may be associated with lesions about the hypophysis and floor of the third ventricle is abundant. In about 7 per cent. of the cases of interpeduncular tumors so frequently associated with Fröhlich's syndrome the patients have some time during the clinical course diabetes insipidus. Bullets lodged in this position, secondary carcinomas of the infundibulum, and basal skull fractures involving the area above mentioned not infrequently give rise to polyuria.

This polyuria was naturally supposed to be due to increased secretion of the pars intermedia when these extracts were shown by Magnus and Schaefer to have a diuretic action. Recent work seems to indicate that the cause of this polyuria is not dependent upon altered or increased secretion of the pars intermedia. The control of diabetes insipidus by pituitrin speaks forcibly at least against overactivity of the cells of the pars intermedia as the cause of this disease.

As hypophyseal extracts and epinephrin have so many actions in common it was quite natural to suppose that they might have a similar effect upon sugar metabolism.

Experimental work which has been done, especially by Cushing and his school, would seem to indicate that overactivity of the pars intermedia might be followed by a decreased sugar tolerance, giving rise to glycosuria, so frequently observed in acromegalics. Lessened or inhibited secretion of the pars intermedia would give rise to increased sugar tolerance. This

increased sugar tolerance would lead to an excess of fat such as is observed in dystrophia adiposogenitalis. In most of the experiments the conclusions have been drawn after feeding patients or experimental animals sugar by mouth. The most accurate studies would naturally be made in those experiments in which known amounts of sugar were given intravenously.

The glycosuria which accompanies hypophyseal operations is light and transitory, disappearing in from 24 to 36 hours after the operation.

Camus and Roussy came to the following conclusions concerning glycosuria:

(a) The different interventions practiced upon the pituitary body, partial removal of one or both lobes or total removal do not modify in an appreciable degree the tolerance to carbohydrates nor the appearance of alimentary glycosuria.

(b) The injections of concentrated extracts of the posterior lobe, the anterior lobe or of the whole hypophysis do not sensibly modify in the animals operated on the limit of tolerance to carbohydrates.

The Pharmacology of Hypophyseal Extracts . . . . . .

Frederick S. Hammett

Introduction—Chemical Composition of the Hypophysis—Effects of Hypophysis Feeding on Metabolism—Effects of Hypophysis Feeding on Growth and Sexual Development—Effects of Whole Gland Extracts on Blood Pressure—Effects of Whole Gland Administration in Man—Pharmacology of the Anterior Lobe—Isolation and Properties—Effects of Thetelin on Growth—Clinical Use of Tethelin—Effects of Anterior Lobe on Metabolism—Pharmacodynamic Effects of Anterior Lobe Extracts—Pharmacology of Pars Tuberalis—Pharmacology of Pars Intermedia—Pharmacology of Posterior Lobe—Pharmacodynamic Effects of Posterior Lobe Extracts—Effects of Posterior Lobe on Metabolism—Effects on Secretions and Lactation.

The Pharmacology of Hypophyseal Extracts

FREDERICK S. HAMMETT

PHILADELPHIA

Introduction

A strict interpretation of the term pharmacology would limit this discussion to a consideration of the action of hypophyseal extracts as drugs. Such a limitation would, by its elimination of much allied biochemical and physiological information, so narrow the conception of the nature of the action of these extracts that only a meager understanding of the phenomena concerned could be obtained. Consequently, as the occasion arises, there will be introduced into the subject matter brief descriptions of evidence obtained from the allied fields of the other medical sciences, in order to throw as much light as possible on the problems and results involved.

No preliminary description of the anatomy, gross or microscopic; the evolution or the development of the hypophysis is necessary, since these phases have been thoroughly covered in the monographs by Cushing (1912), Houssay (1918) and Bell(*b*) (1919). For purposes of convenience the order of presentation of the material will begin with the studies made of the hypophysis as a whole. Attention will then be directed to the anterior, intermediary and posterior portions respectively.

Since later work has demonstrated that the reactions obtained by the use of extracts of the hypophysis depend upon the source of the extract; that is to say whether the extract is made from the anterior or from the posterior lobe substance, these earlier studies of the gland as a whole have largely an historical interest.

Chemical Composition of the Hypophysis

As far as the chemical composition of the hypophysis is concerned but little of pharmacological value is reported. Costelli (1914) made an extensive study of the lipoid materials and Fenger(*a*) (*b*) (1915) of the water, ash, phosphoric acid and ether-soluble substances of the gland.

The latter investigator was unable to detect any distinct seasonal variations in these constituents. Malcolm (1904) determined the nitrogen, phosphorus and calcium content of fresh ox pituitaries and found the following percentages present:

	Anterior Lobe	Posterior Lobe
Nitrogen	13.3	12.3
Phosphorus	0.72	0.8
Calcium	0.123 whole gland.	

When attention was drawn to the fact that an enlargement of the hypophysis is a frequent sequel of athyroidism, either experimentally produced as by Rogowitsch (1889), Degener and Livingston (1913) and others, or induced by pathological conditions as recorded by Schöneman (1892), Comte (1898) and others, the theory of a compensatory hypertrophy and vicarious functioning of the hypophysis for the thyroid came into vogue and still has Larson (1920) as a supporter. This led to a search for iodin in the pituitary, since the main factor of thyroid function was supposed to be iodin, and consequently, if the hypophysis took over the thyroid function when this latter gland was pathological, iodin should of necessity be found therein as an indication of its pharmacological worth and physiological function. Early results were conflicting. Baumann (1896) failed to prove the presence of iodin in the glands he tested. Schnitzler and Ewald in the same year obtained positive results as did Wells a year later. In 1909 Halliburton, Candler and Sikes, and Simpson and Hunter reported that they were unable to find iodin in human or other pituitary glands and the suggestion was made that possibly the previous positive findings had been due to the ingestion of iodin-containing compounds by the subject examined. Wells(*b*) (1909-10) then made a comparative study of the iodin content from such sources and came to the conclusion that the presence of iodin in normal pituitary glands was unproven. This was definitely confirmed by Denis (1911) for the human and by Seamen (1920) for the sheep. The only conclusion justified from these observations is that the effects produced by pituitary extracts cannot be attributed to this element, nor can the hypophysis be considered on the basis of any iodin containing compound as functioning vicariously for the thyroid. Nevertheless, the findings of Renon and Delille(*a*) (1908) and of Crowe, Cushing and Homans(*b*) (1910) of marked changes in the thyroid after injections of whole pituitary extracts and hypophysectomy respectively do indicate that there may be some interrelation between the two glands.

It is probable, however, that these changes observed in the one gland as sequelæ of disurbances in the other indicate a metabolic disorder generally distributed throughout the organism. I do not wish to be considered as denying the probability of a supplementary effect of the secretions of these two glands, upon the organism as a whole, but must emphatically

assert that we have no evidence demonstrating or even indicating that the one gland can take upon itself the specific and individual functions of the other.

The evidence of a generalized effect is ample. Comte (1898) and Erdheim and Stumme (1909) observed that the hypophysis tends to enlarge in pregnancy, a condition in which altered metabolism is evident, but also a condition in which thyroid enlargement has been noted.

Pharmacology of the Hypophysis

Effects of Hypophysis Feeding on Metabolism.—The effects on metabolism of feeding pituitary glands are similarly indicative. When Schiff (1897) administered desiccated pituitary substance to a normal human subject, to an acromegalic and to a patient having paralysis agitans, he failed to detect any changes in the nitrogen output of any of his subjects, but did obtain an increased phosphorus excretion from the two diseased individuals. Moraczewski (1901) in his experiments on animals observed both an increased nitrogen and phosphorus excretion accompanied by a possible calcium retention. Oswald (1902) fed the gland substance to dogs and got no effect on metabolism. Malcolm (1904) carried out an extensive series of investigations, the results of which seemed to indicate an increased nitrogen output and calcium retention. Thompson and Johnson (1905-06) reported a stimulation of the metabolism expressed in an increased nitrogen and phosphorus elimination, while Franchini (1910) found disturbances of calcium and magnesium metabolism, which supported Cerletti's (1907) observations that the administration of hypophyseal substance retarded bone growth. Schäfer(*b*) (1912) could find no changes in metabolism though he seems to think that he obtained indications of an increased calcium and magnesium excretion. Recent work by Hammett, Patten and Suitsu (1920) has shown that the administration of small amounts of pituitary substance to man causes an increase in the blood uric acid which continues long after the drug has been stopped.

Effects of Hypophysis Feeding on Growth and Sexual Development.—Studies of the results of induced hyperpituitarism also demonstrate a generalized rather than a specific effect. The experiments of Sandri (1909), Goetsch(*a*) (1916), and others have shown that a definite retardation of growth occurs, though Schäfer(*a*) (1909) did not obtain this result. While the hypophysis feeding retards growth it apparently stimulates an increase in growth and activity of the generative tissues of both male and female as Mayer (1910) and Goetsch(*a*) (1916) have shown, though Simpson (1920) failed to obtain any increased egg production in fowls under such treatment. As far as the activity of the secondary sexual organs is concerned Gavin (1913) was unable to obtain any consistent increase in mammary activity after the oral, subcutaneous or intravenous

administration of extracts of the whole gland, though he did get by the latter method an occasional accumulation of milk in the lower part of the udder. When the hypophysis is removed from young animals by surgical procedure gross disturbances in development appear as the experiments of Allen (1917), Smith(*a*) (1917), Cushing(*b*) (1912) and others have shown; and Sweet and Allen(*a*)(*b*) (1913) found marked structural changes in the pancreas, testicles, thyroid and other tissues of their operated dogs.

All these results indicate that the secretion of the hypophysis as a whole, contributes to the maintenance of the regulation of the organic and metabolic processes in general. They do not justify, in fact they detract from, the opinion that the hypophysis is a gland the secretion of which is specifically effective for any particular or individual tissue or organ in the sense of a vicarious functioning.

Effects of Whole Gland Extracts on Blood Pressure.—Early attempts to determine the physiological activity of hypophyseal extracts on blood pressure were made by Oliver and Schäfer (1895). They observed a rise of blood pressure which was maintained for some time. On the other hand Syzmonowicz (1896) found that injections of extracts of the whole gland resulted in depressor effects and a weakening of the heart beat. Howell(*b*) (1898) then demonstrated that the pressor effect was not a property of the whole gland but was due to some constituent of the posterior lobe. This finding was confirmed by Schäfer and Vincent (1899-1900), Führer (1913) and others and will be described in detail later.

Effects of Whole Gland Administration in Man.—The effectiveness of the hypophysis as a therapeutic agent is bound up with the sum total of the reactions induced by its component parts and it appears as if certain pathological states respond better to the administration of the whole gland than to the ingestion or injection of preparations of the separate lobes. Hofstätter(*g*) (1920) and Dalché (1919) comment favorably upon its use in metrorrhagia and the menopause. The latter prefers the oral route of administration in these conditions and reports that when two to four doses are given each day improvement results. Nevertheless, the treatment must be continuous else a relapse occurs. Timme(*a*) (1918) and Pardee (1919) recommend the use of preparations of whole pituitary gland in doses of from one half to three grains three times a day in the treatment of the so-called pituitary headaches. Similar medication is indicated in cases presenting symptoms of both anterior and posterior lobe deficiency as described by de Schweinitz and How (1917) and others, while Beck(*c*) (1920) reports that certain types of cachexia are also benefited by such treatment.

Pharmacology of the Anterior Lobe.—Cunningham (1913) in his description of the anatomy and embryology of the anterior lobe of the hypophysis states that this portion of the gland may be regarded as the

functional part of the hypophysis. Such a limiting conception is not substantiated by the mass of evidence that has accumulated. This has conclusively demonstrated that the posterior lobe and possibly the intermediary portion also produce secretions of importance to the organism. Nevertheless, the function of the anterior lobe in the animal economy is unquestionably great, and recent studies have shown that its active principle, "tethelin," has a valuable place in therapeutics.

Effects of Anterior Lobe on Growth. The discovery and isolation of this active principle was the development of many studies of the effects on growth of the administration of extracts or substance of the anterior lobe to various animals. Cerletti (1907), Etienne and Parisot (1908), Sandri (1909), Cushing (1912) and others, all reported a retardation of growth as a result of the ingestion or injection of hypophyseal extracts in young animals. Aldrich(*b*) (1912-13) compared the effects on growth of young white rats of extracts of the posterior and anterior lobes and demonstrated that the retardation effect could be attributed to the action of the anterior lobe. Wulzen(*a*) (1914) found that the growth of young fowls was retarded by the addition to their diet of fresh unmodified anterior lobes of ox pituitaries as determined both by the lesser increase in body weight and length of the long bones. This was supported by similar studies of Pearl (1916), while Maxwell (1916) found that the retardation of growth was not prevented by the administration of thymus substance to the animals ingesting the anterior lobe. Similar results are reported by Lewis and Miller (1913) and White and Titcomb (1914).

On the other hand Schäfer(*a*) (1909) noted that apparently an acceleration of growth could be obtained if the substance was fed to animals after they had passed through their early growth period and were about half grown. The variability of the results gave rise to the opinion proposed by Robertson (1916) that the precise nature of the growth influence of the anterior lobe "may be expected to be considerably affected by the stage of development of the animals to which the gland is administered. This view, indeed, finds ample confirmation in the diversity of clinical manifestations of pituitary insufficiency and the profound extent to which, as Cushing (1912) has exhaustively shown, these manifestations are modified according to whether the pituitary insufficiency or hyperactivity are pre-adolescent or post-adolescent in origin." This belief he confirmed in a series of carefully controlled experiments in which he found that the growth of mice was retarded or accelerated according to whether the anterior lobe substance was fed early or later in the life of the experimental animals. This principle of a differential effect depending on the age of the animal at time of administration of the effective substance is supported by Wulzen(*a*) (1916) in her study of fission of planarian worms, and is strengthened by a recent report of Marinus (1919).

Effects of Anterior Lobe on Gonadal Activity.—The administration of

anterior lobe preparations produces certain changes in gonad activity. Concise allocation of gonadal disturbances in connection with pituitary disorders to the anterior lobe was first made by Cushing(*a*) (1909) when he attributed the clinical condition of dystrophia adiposogenitalis to hypofunctioning of the part of the hypophysis. Increased sexual activity as a result of anterior lobe administration was shown by Aschner(*b*) (1912), and Goetsch and Cushing (1913). This was not obtained when posterior lobe extracts were used. In a later series of experiments Goetsch(*a*) (1916) was able to demonstrate a sexual precocity in his animals. Studies on egg production and hatchability by Clark (1915) seemed to show that these phenomena were heightened by the addition of anterior lobe to the diet of the domestic fowl, though Pearl and Surface (1915) and Pearl (1916) failed to obtain such an effect. Frank (1919) also failed to obtain evidence demonstrating a consistent effect on the genitalia of the administration of anterior lobe extracts. Notwithstanding these latter negative results clinical and other evidence sufficiently supports the belief that the anterior lobe may in some way be concerned in gonadal activity.

Isolation and Properties.—*"Active Principle" of Anterior Lobe.*—We now turn to the active principle that presumably is the main factor concerned in the production of the changes that have been described. To Robertson (1916) is due the credit for the isolation of this compound. The method of preparation as evolved by him is rather simple. The anterior lobes are ground up in a mortar with three times their weight of a mixture of equal parts by weight of anhydrous sodium and calcium sulphates and the whole is dried on a water bath for about an hour. This mixture is pulverized and extracted with absolute alcohol at the boiling temperature for forty-eight hours. The extract, after filtration, is evaporated to a small volume under reduced pressure, cooled and mixed in a cylinder with one and one-half times its volume of dry ether. After standing for several hours a flocculent precipitate settles out. The supernatant liquid is siphoned off and the residue is mixed with a large volume of a mixture of one part by volume of absolute alcohol, and one and one-half parts of dry ether. The precipitate is rapidly filtered off by suction and dried at 30-35° C. for twenty-four to forty-eight hours. The resultant product is a dry, cream-colored powder, which is kept in thoroughly dry glass containers on account of its hygroscopic properties. The substance is apparently a chemical unit from the fact that its nitrogen and phosphorus content are constant and has been named tethelin, from the Greek root τεθηλως, growing. When the compound prepared in this manner is exposed to the air it becomes dark in color. When heated it begins to darken at a temperature lying between 100 and 110° C. Tethelin is soluble in water to the extent of about five per cent, forming at that concentration a brown, turbid solution. More dilute solutions are paler in color, and one per cent solutions are but slightly opalescent. The com-

pound is soluble in ethyl alcohol, ether, chloroform and carbon tetrachlorid. Aqueous solutions are faintly acid. Tethelin contains 1.41 per cent of phosphorus and 2.58 per cent of nitrogen. The aminonitrogen content is 1.24 per cent and increases on hydrolysis. The compound has a saponification value of about 87 mg. of KOH per gram of substance and a mean iodin absorption value of 33.2 per cent. In aqueous solutions no biuret reaction is given: the Millon reaction is atypical. It does not reduce Fehling's solution either before or after hydrolysis with barium hydroxid or barium dioxid followed by sulphuric acid. It gives Ehrlich's reaction indicating the presence of an acetylated oxyamino group. Wiedel's reaction is positive, indicating the probable presence of an iminazolyl radical. When tethelin is decomposed by mild hydrolysis inosite is found among the products of the reaction. The occurrence of this compound as a component of tethelin is particularly interesting from the fact that it is a normal constituent of the rapidly growing parts of plants.

Effects of "Tethelin" on Growth.—Having obtained this compound as an extract of the anterior lobe of the hypophysis Robertson(*b*) (1916) compared its effects on the growth of white mice with the effects produced by feeding anterior lobe substance as a whole, and came to the conclusion that "the effects of tethelin upon the growth of white mice resemble in every particular the effects of the administration of the whole anterior lobe." Later Robertson and Delprat (1917) found that tethelin when fed to the mothers of suckling mice was apparently not secreted by the mammary glands since the growth of the young was unaffected while suckling, but when the compound was added to the diet of the animals at weaning growth was immediately accelerated.

A similar identity in the effect of the anterior lobe substance and tethelin was observed when studies on the growth of carcinomata were made. Robertson and Burnett(*a*)(*b*) (1915) had found that the injections of extracts or emulsions of the anterior lobe cause an increase in the growth-rate of the primary tumor in rats inoculated with carcinoma at certain states, though no enhancement of metastatic tendency was observed. When these same workers (1916) injected tethelin instead of the emulsions of anterior lobe into carcinomatous rats a rapid growth of the primary tumor was observed and the additional effect was produced of an increased tendency to metastatic involvement.

The attempts at correlating this growth-promoting effect of tethelin with some specific group or radical of the compound have so far been unsatisfactory, though Robertson and Burnett(*c*) (1918) have obtained evidence pointing to the possibility that the presence of an hydroxyl group in the molecule may be the effective point of attack.

Although the evidence accumulated by Robertson and his coworkers undoubtedly indicate that in tethelin there has been produced a substance possessing the same growth-promoting functions in concentrated form as

does the anterior lobe of the hypophysis, yet the proof that tethelin is a distinct chemical entity is anything but clean-cut and conclusive. This, however, does no detract from the fact that there has been developed a method for the preparation of a concentrated substance the therapeutic applications of which are promising to be of considerable value.

Not only does tethelin accelerate body growth and growth of carcinomata, but it also hastens tissue repair as expressed in the replacement of tissue after inanition or in the healing of granulating wounds as shown by Robertson(*d*) (1916). Such findings immediately open up the possibility of its therapeutic value in such conditions. A study of the pharmacology of the substance by Schmidt (1917) showed that its therapeutic application is unaccompanied by harmful effect. Robertson (1916) had already shown that the intravenous administration of tethelin does not cause any appreciable rise in blood pressure, but "very large doses (5 mg. per kilo.) dissolved in physiological saline and injected into rabbits lead to a slight and transient fall in blood pressure, followed in a few minutes by a return to normal and a slight increase in amplitude of the heart beat. Repeated administrations of this dose at intervals of a few minutes lead on each occasion to a transient fall of blood pressure, while the amplitude of the heart beat increases considerably." The effect in any instance is not nearly so great as that produced by the inhalation of a whiff of amyl nitrite. The intravenous injection of tethelin does not cause diuresis. Schmidt (1917) showed that no alexin-fixation was obtained in rabbits given six intravenous injections of 50 mg. each of tethelin dissolved in salt solution over a period of two weeks, and bled ten days after the last fixation. He also found that the compound is incapable of acting as the antigen in the Wassermann test; that it is non-toxic when injected intraperitoneally in 100 mg. doses into the guinea-pig; that it causes no abnormal temperature changes when thus administered; that when intravenously injected no effect on the blood proteins is produced as determined by the refractometric method: that it does not markedly stimulate leucocytosis; that it can serve as a medium for the growth of B. coli and B. proteus but not for B. bulgaricus; that it is not split by lipase or trypsin and that it does not stimulate contraction of the isolated uterine segment of the cat or guinea-pig.

Clinical Use of Tethelin.—This work having shown that tethelin is both non-toxic and non-antigenic and is hence therapeutically without danger, Barney (1917-18) studied its action on indolent ulcers of several types. With one exception it was not used in any case where the usual ointments and stimulators of granulation tissue had not been extensively tried without success; nor was it used in luetic ulcers. The treatment consisted in applying tethelin in solution on gauze or as a powder directly to the sore. In all six of the reported cases improvement or cure was obtained. Mayo (1918) also employed combined injections and applications of tethelin to a burn caused by electrical discharge and obtained a cure

within ten days. She used 100 mg. as the daily dose divided between the two methods of administration. Experimental endeavors to inhibit the progress of tuberculosis in guinea-pigs by the injection of tethelin have so far been unsuccessful. Corper (1915) got no effect either in the duration of life, development, recession or rupture of the intracutaneous tubercles produced by dead human bacilli.

Effects of Anterior Lobe on Metabolism.—The studies of the effects of the administration of the anterior lobe of the hypophysis on metabolism are few and contradictory. Malcolm (1904) found that the desiccated substance caused a nitrogen retention and an increased calcium output, while White and Titcomb (1914) reported a lesser calcium and phosphorus urinary content under similar conditions, and Titcomb (1913-14) ob-

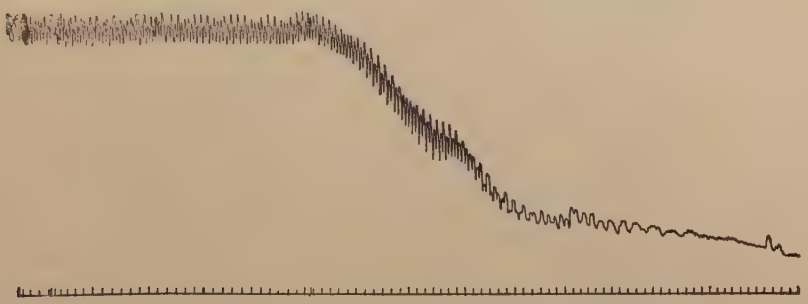


Fig. 1. Showing the drop in arterial pressure induced by the injection of an extract of the anterior lobe of the hypophysis. (After Hamburger, Am. J. Physiol.)

served an increased calcium and phosphorus excretion in cancer patients as a result of the administration of anterior lobe substance. Hewitt(*a*)(*b*) (1915) concluded that the administration of small amounts of pars anterior of the ox together with thyroid tissue has little if any influence on the action of the thyroid as given alone.

Pharmacodynamic Effects of Anterior Lobe Extracts.—The effects of extracts of the anterior lobe on blood-pressure in moderate doses are generally minor in degree and tend towards a transient lowering as shown by Halliburton, Candler & Sikes (1909). A similar effect was demonstrated to follow tethelin injections by Robertson (1916). Howell(*b*) (1898) early showed that the pressor effect was not obtained from this portion of the hypophysis, and his results have been amply confirmed. On the other hand, Hamburger(*a*)(*b*) (1904) found that when saline extracts of the anterior lobe are intravenously injected they produce a decided fall in pressure, accompanied by an acceleration and weakening of the heart-beat. He confirmed these observations in 1910 and considers that his decidedly positive results as opposed to the negative ones of Oliver and Schäfer (1895) are due to the fact that these workers destroyed the depressor substance by their method of preparation of the extract. This is supported by

the fact that when he himself prepared an extract by their method he too failed to obtain a depressor effect. Hence, it is evident that extracts of the anterior lobe as ordinarily prepared and given in moderate doses have little if any action on blood-pressure, though Motzfeldt (1917) claims to have obtained an antidiuretic action as a result of its administration. No physiological action on the intestine could be obtained by Shamoff (1916-17) in her studies of these extracts.

On account of the probable presence of an iminazolyl group in tethelin Robertson (1916) was inclined to believe that the compound is related to the physiologically active substances of the posterior lobe of the pituitary body, which too is supposed to contain this grouping. Although tethelin as isolated does not cause the characteristic responses in blood-pressure and diuresis that are obtained by posterior lobe extracts, when Schmidt and May (1917) hydrolyzed the compound by barium hydroxid the resultant solution was found uniformly to cause contraction of the isolated uterus of the virgin guinea-pig, and a slight rise in the blood-pressure of rabbits. These authors, therefore, consider that the active substance of the posterior lobe of the pituitary body is largely derived from a splitting of a substance which is a product of the secretion of the anterior lobe and which contains an iminazolyl radical, inferentially considering tethelin as this precursor.

Pharmacology of the Pars Tuberalis.—Before going on to a consideration of the pars intermedia of the hypophysis, it is necessary to give a brief description of the studies of the pars tuberalis of the hypophysis first histologically described by Tilney(*b*) (1913). This structure is apparently a constant component of the hypophysis distinct from the pars anterior, pars intermedia and pars posterior and consists of an epithelial investiture of the neural stalk having a distinct embryological origin, as shown by Atwell (1918) in the rabbit. Investigations of the possible pharmacodynamic activity of this portion of the hypophysis were undertaken by Atwell and Marinus (1918), because both anterior lobe and posterior lobe preparations are frequently contaminated by its inclusion. These authors separated the pars tuberalis from the other parts of the hypophysis, but were unable to obtain any evidence of the presence of an oxytocic or pressor principle in sufficient amounts to justify the assumption that this cellular group is a physiologically functional part of the posterior lobe. In a series of experiments conducted by Marinus (1919) in which the effects on growth of the anterior lobe and the pars tuberalis were studied no alterations were observed in the animals having had the latter substance administered to them, from which he came to the conclusion that no anterior lobe functions can be attributed to the pars tuberalis.

These brief studies would lead to the opinion that this histologically and embryologically distinct part of the hypophysis takes no part in the functions of the other portions of the gland as exhibited by the pharmacological activity of their extracts.

Pharmacology of the Pars Intermedia.—The histology of this portion of the hypophysis has been recently studied by Lewis and Maurer (1920). From their report it is evident that there are histological indications of a physiological activity of a secretory glandular nature in this portion of the hypophysis which tends to afford a morphological confirmation of the pharmacodynamical investigations of earlier workers.

There has been and still is some little controversy over whether or not the pressor, uterine-contracting and milk-secreting stimulating effects

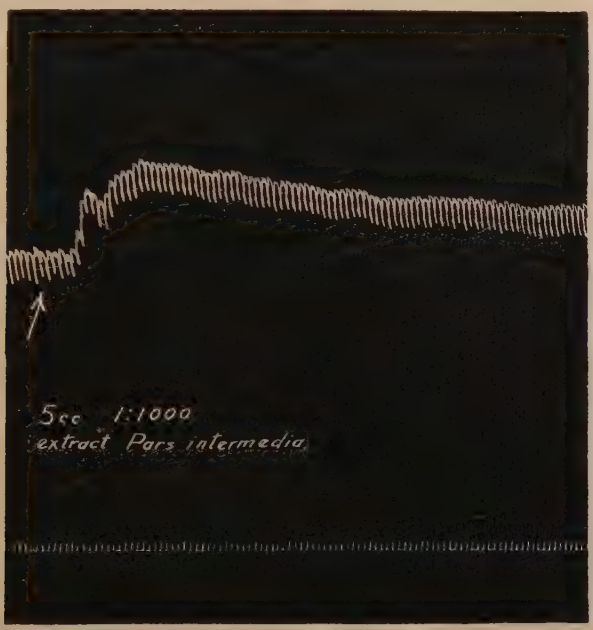


Fig. 2. Showing the effect upon the blood-pressure of the rabbit following the intravenous injection of pure pars intermedia extract. Time is in seconds. (After Atwell and Marinus, Am. J. Physiol.)

produced by extracts of the posterior lobe of the hypophysis are due to the simultaneous inclusion in the preparations of extracts of the pars intermedia. The source of the opinion that such a probability exists is due to the fact that Lewis, Miller and Mathews (1911) in a careful study of the action of extracts of the various parts of the hypophysis found that extracts of the pars intermedia caused a rise in blood-pressure of the experimental animals analogous to that produced by the usual posterior lobe extracts. These results were confirmed by Biedl(*a*) (1912). This pressor effect was also obtained by Atwell and Marinus (1918). Herring(*f*) (1914), however, was unable to obtain any such pressor effect from extracts with Ringer's solution of the isolated pars intermedia as he obtained from his posterior lobe extracts, but did get an initial fall in pressure which lasted but a very short time. Yet he found that his extracts

exerted a contractor or oxytocic effect on the virgin rat uterus. He attributes this to the possibility of a greater sensitivity of the uterus to any potent extract since "the contraction of uterine muscle is a simple matter compared with the variety of factors which are concerned in the general rise of blood-pressure, and it well may be that a vastly greater amount of the active principle is necessary to produce a rise of blood-pressure than will suffice to bring about contraction of the uterus. It may be, too, that the active material exercises a selective effect upon uterine muscle." Nevertheless, since Schäfer and MacKenzie (1911) have shown that extracts of the pars intermedia may act as galactagogues there is a possibility that the active principle that produces this and the oxytocic effect is different from that concerned in the rise in blood-pressure, increased volume of the kidney and diuresis, and is a constituent of the pars intermedia. Herring (1914) also found that extracts of the pars intermedia did not cause expansion of the kidney nor diuresis while they did tend to stimulate a slight milk secretion. He then makes the assumption that the *active* principles, presumably of the posterior lobe, have their origin in the cells of the pars intermedia, the epithelial cells of which secrete a thin colloid material which finds its way into the pars nervosa and is there stored as a hyaline material.

Herring (1914) extended his observations upon the activity of the extracts of the pars intermedia to a quantitative comparison of equivalent extracts from this portion and the pars nervosa of the hypophysis. He found that the pars intermedia contained but from one-half to one-fifth the amount of uterine contracting substance obtaining in the posterior lobe and confirmed his previous results on the inability of extracts of the pars intermedia to cause an increase of kidney volume, diuresis or rise in blood-pressure. As far as the kidney effect is concerned, Motzfeldt(*a*)(*b*) (1917) has reported that the effects of oral administration of pars intermedia indicate the possession of an antidiuretic action. Shamoff (1915-16) did not obtain any reaction with pars intermedia when using intestinal segments as the test object.

From these experiments it would appear as if the pars intermedia of the hypophysis does contain a substance or substances capable of causing contraction of the isolated virgin uterus and stimulating mammary secretion. Such an oxytocic principle was shown by Schmidt and May (1917) to result from the barium hydroxid hydrolysis of tethelin and it has been proven that extracts of the posterior lobe of the hypophysis exert a similar action.

It would appear as if a uterine-contracting principle is in some form or other a constituent of all parts of the hypophysis. Since Abel and Kubota (1919) have found that histamin, a uterus-contracting substance, is present in practically all tissues of the body, perhaps this is the cause of the reaction from extracts of the pars intermedia.

While the studies just reported fail to give conclusive evidence that the pars intermedia of the hypophysis is a definite source of the active principles commonly attributed to the posterior lobe, they do seem to afford evidence favoring the hypothesis that the substance giving rise to the contraction of uterine muscle is not the same substance that causes the blood-pressure changes.

From the clinical point of view Barker and Mosenthal (1917) and Barker and Hodge (1917) have been of the opinion that diabetes insipidus may possibly be due to an underfunction of the pars intermedia of the hypophysis cerebri rather than to hyperpituitarism. They have reported successful results obtained in that disorder by the daily subcutaneous administration for four days of one cubic centimeter of a pituitary preparation containing extracts of both the pars posterior and pars intermedia. The dose was then increased, but was not rigidly followed in every case. The patients were kept comfortable and excreting a normal amount of urine and of normal specific gravity under this treatment. The authors, however, do not stress the idea that the disorder is due to a disturbance of the pars intermedia and advocate the keeping of an open mind on the subject.

Pharmacology of the Posterior Lobe.—*Active Principles. Isolation and Properties.*—The reports of McCord (1915) and Fenger (1916) indicate that the production of the active principles by the posterior lobe begins at an early age, since extracts from fetal hypophyses give the characteristic pressor responses when tested. The latter investigator is of the opinion that the activity of the lobe is somewhat enhanced during the growing period. Herring (1908) has made an extensive study of the activity of extracts from the hypophysis or the posterior lobe of various types of animals and his results taken in conjunction with those of Fenger (1916), Lieb (1914-15) and others give proof that similarly acting substances, as tested pharmacologically, are the common property of the gland as found in a wide range of animals. The exact chemical nature of the active principles of the posterior lobe extracts is as yet unknown. Abel and Kubota (1919) were able to isolate β-iminazolylethylamin from the posterior lobe and consider that this compound, called histamin for convenience, is the plain muscle stimulating constituent of pituitary extracts. But since they were able to prove its presence in all tissues of the body they admit that it is not specific to the hypophysis. They adduce as evidence that histamine is the smooth muscle contracting substance of posterior lobe extracts, the fact that it causes a similar type of response of uterine muscle as do the extracts themselves as was earlier noted by Niculescu (1914), Roth(*a*)(*b*)(*c*) (1913-14) and others. There is, however, evidence that this compound is not a specific active principle of such extracts. Although Guggenheim(*a*) (1912), Führer (1913), Cow(*b*) (1919) and others base their primary objections to the idea of the identity

of histamin with the uterine contracting principle on the fact that they obtained a relaxation of the rat or mouse uterus with histamin and a contraction with posterior lobe extracts, Abel and Macht (1919) showed that this differential effect was probably due to the difference in the relative strengths of the two solutions used, and that sufficiently dilute solutions of histamin gave the same contracting reaction as did the posterior lobe extracts, while concentrated doses of the latter exerted the same paralyzing effect as did large amounts of histamin. In 1913-14 Guggenheim(*b*)(*c*) had noted that there was a difference in stability of posterior lobe extracts and histamin towards alkali. This was confirmed by Dudley (1919) who extended the comparative study of these two preparations. He found that histamin is not destroyed to any marked extent while posterior lobe extracts lose their potency after a very short contact with sodium hydroxid. Moreover, histamin is not destroyed by trypsin under the same conditions that result in the destruction of the uterine-contracting principle of the posterior lobe extracts. In addition histamin can be extracted from acid solutions with butyl alcohol at low pressure only with great difficulty while the active principle of the posterior lobe extracts is easily soluble in this alcohol as it also is in chloroform, while histamin is not conspicuously soluble in this latter reagent. The evidence thus far available speaks against the idea that histamin is the active principle of the posterior lobe concerned in its oxytocic activities. It has been suggested that the presence of histamin in such extracts might be due to a previous bacterial decomposition of the glandular substance before extraction. Hanke and Koessler (1920) having devised a colorimetric method for the determination of histamin in protein and protein-containing materials analyzed a lot of perfectly fresh beef pituitaries weighing three hundred and forty-six grams and were unable to find histamin present. They, therefore, conclude that "perfectly fresh beef hypophysis does not contain histamin," and suggested that the positive findings of Abel and Kubota (1919) might well have resulted from the previous activity of certain putrefactive microörganisms, which as is well known can and do form histamin from histidin, a common constituent of animal proteins. And I can say that from what I have seen of the condition of some of the lots of pituitaries that have been used for the commercial preparation of posterior lobe extracts that such a possibility is a probability if not a certainty. In addition the studies of Jackson and Mills (1919) on the comparative action of extracts of the hypophysis and histamin on the bronchial musculature give further evidences of the physiological difference between the two active principles. Such a possibility is also to be thought of in connection with the studies of Aldrich(*c*) (1915) on the presence of histidin-like substances in posterior lobe extracts.

Watanabe and Crawford (1916) were inclined to the opinion that the active pressor principle of the posterior lobe is adrenin, but their

evidence, based as it is largely upon a similarity of colorimetric reaction of extracts of the two glands is not convincing as to their identity, a fact recognized by the authors themselves. It was shown by Abel and Pincoffs (1917) that the proteoses and albumoses usually present in posterior lobe extracts cannot be considered as the immediate source of the active principles, since after they have been removed the residual filtrate still exerts its characteristic pressor and oxytocic effects.

The attempts at isolating in a pure, identifiable condition the active principles of the posterior lobe have so far been unsuccessful. None of the workers have been able to report the chemical constitution and structure of the various compounds they have obtained. Nevertheless, the studies made have supported the idea that in these extracts there are at least three separate active principles, a pressor, a depressor and a uterine-contracting or oxytocic substance as suggested by Herring (1914), Crawford and Ostenberg(*a*)(*b*) (1914) and others. Aldrich(*a*) (1908) separated from the posterior lobe a basic material in the form of a picrate and a sulphate which had a pressor effect on the blood-pressure. In 1913 and 1914 Führer published several reports of his extensive studies on the isolation of the active principles of the posterior lobe. He was able to obtain a large series of crystalline compounds by first precipitating the protein-free extracts of the material with phosphotungstic acid and then treating the mixture thus obtained so as to obtain the sulphate salts. This mixture he named *Hypophysin* and considered that it contained at least four active principles and possibly eight, the whole containing all the physiological and pharmacological properties of the extracts themselves. Badouin (1913), Crawford and Ostenberg (1913-14), Claude and Porak (*b*) (1914) and Houssay(*a*) (1915-16) attempted the isolation and purification of the active principles by means of precipitation with lead subacetate but were unable to get satisfactory yields of identifiable compounds. Heidelberg and Pittenger (1914) reported a preliminary study of efforts to obtain the active principles as metallic salts, such as aluminum, but nothing further has definitely been obtained. Bouin and Ancel (1914) prepared a crystalline sulphate that had all the properties of the original extract and later Ancel and Bouin (1914) obtained what they considered to be the pure base. Their method consisted in fixing the posterior lobes in a mixture of equal parts of alcohol and ether for eight to ten days and then macerating the tissue in distilled water. The liquid was then pressed from the mass, filtered and clarified with ammoniacal lead acetate. The filtrate was a clear liquid. It was treated with lead hydroxid, filtered, and the process twice repeated. The bases were then precipitated by silver nitrate. The precipitate was treated with dilute ammonia water, filtered, and the filtrate rapidly evaporated. This process yielded a crystalline compound which they claimed was the silver salt of the base. When this was decomposed by hydrogen sulphid the base was obtained as such in

solution. When the lead hydroxid filtrate was quickly evaporated without the addition of silver nitrate a substance was obtained that after repeated solution in methyl alcohol and precipitation by anhydrous ether yielded a crystalline product. This they consider to be the true base because of its characteristic pharmacological reactions. Nevertheless, they failed to report any chemical analysis of the compound. A recent study by Fenger and Hull (1920) was unsatisfactory.

The methods of manufacture of the commercial extracts of the posterior lobe are not particularly complicated. One of them consists in macerating the finely ground tissue for four hours with a strongly diluted solution of acetic acid at a temperature just below the boiling point of water. The extract so obtained is filtered from the residual tissue till clear, sterilized by passing through a Berkefield filter candle and put up in suitable sterile containers for marketing. There is considerable loss of active principle, as measured by the oxytocic reaction, during this process. Adams (1917) made a study of the conditions leading to destruction of the active compound and found that the substance is destroyed at the temperature of boiling water when the hydrogen-ion concentration is $N \times 10^{-5}$ but that the compound is stable at the greater acidity of $N \times 10^{-3}$. From the fact that the rate of destruction proceeds in a manner characteristic of a single substance decomposing according to the law of a monomolecular reaction, it is evident that the determination of the strength of posterior lobe extract on the basis of its oxytocic effect represents an evaluation of a single substance and is valid for the measurement of this principle. This substance may not be the pressor compound.

Inasmuch as the question has arisen whether or not the small amounts of alcohol left in the syringe after sterilization destroy the physiological activity of the extract Hamilton (1918) and Pittenger (1918) investigated this possibility and found that the addition of reasonable amounts of alcohol to the extracts caused no diminution in their activity.

Assaying Posterior Lobe Extracts. There have been three main methods advocated for testing the pharmacological or therapeutic value of posterior lobe extracts. The observations of Dale and Laidlaw (1912-13) that extracts of the posterior lobe cause contraction of the isolated uterus of the virgin guinea-pig was the starting point not only of the use of such extracts in clinical practice, but also of the use of this tissue as a test-reagent for determining the strength of the extracts used. Although these workers found that the application of equal amounts of the extract to the same uterine segment caused an almost equal amount of contraction it remained for Roth(*a*)(*b*)(*c*) (1913-14) to establish β-iminazolylethylamin hydrochlorid as the standard substance with which the activity of the posterior lobe extracts could be compared, which standard has been accepted as the official method of the United States Pharmacopœia. The

standard relation that has been adopted is that a solution of posterior lobe extract in one to twenty thousand dilution shall give an equivalent contraction effect as measured by the height of the line traced by the point of a lever on the blackened surface of a kymograph as is obtained from a similar amount of a one to twenty million dilution of pure crystalline β-iminazolylethymin hydrochlorid. The method in general consists in suspending an isolated uterine segment from a virgin guinea-pig in a glass cell containing Ringer's solution through which a stream of oxygen is continually passing, and surrounded by a bath kept constantly at body temperature; the segment is so attached to a writing lever that a record

Fig. 3. Showing the oxytocic effect of posterior lobe extract on the uterus *in situ* and the similar type of response induced by histamin. (After Jackson and Mills, J. Lab. & Clin. Med.)

can be made of its movements. Apparatus for use in this test has been devised by Roth (1914), Pittenger (1918), Hammett (1921) and others. That of the latter is probably as simply constructed as any. When the uterine segment has shown by its rhythmical contractions that it is in a suitable condition for use, the height of contraction induced by the previously mentioned dilutions of the standard and the extract to be evaluated are compared and the results deduced therefrom. Of late it appears as if the manufacturers of this product have succeeded in getting a more potent extract that is frequently several times stronger than the U. S. P. requirements. Pittenger (1917), Pittenger and Vanderkleed (1917), and Eckler (1917) have called attention to this and suggested that the official requirement be altered.

Another method of testing the efficacy of posterior lobe extracts is that of measuring the rise in blood-pressure induced in an experimental animal by the intravenous injection of the extract. This method is advocated

by Hamilton and Rowe (1916) as better than the isolated uterus test because frequently the uteri used are variable in their response. Heidelberg and Pittenger (1914) and Pittenger (1917) consider that the blood-pressure method is inherently faulty not only on the basis of Herring's (1914) idea of a greater uterine sensitivity to potent extracts, but also on the basis of the presence of both pressor and depressor substances in such extracts, the algebraic sum of the effect of which is recorded by the

Fig. 4. Graph showing concordant results obtained from the application of repeated doses of an equal amount of pituitary extract to the isolated uterus of the virgin guinea-pig. (After Pittenger, Biochemic Drug Assay Methods.)

pressor method while no indication is given of the oxytocic value. This argument is supported by the observations of Adams (1917) already reported. As far as the irregularity of response of the uteri is concerned it would appear from the study of Hatai and Hammett (1920) as if the factors of heat, age and previous emotional conditions of the test animals are among the causes of variability, and that these disturbing factors can be eliminated by a proper choice of animal for the test.

Spaeth(*a*)(*b*) (1918) raises objections to both the isolated uterus method and the pressor method on the basis of a hyper- and hyposensitivity respectively. He reports experiments in which he used the melanophores of Fundulus heteroclitus as the test-object; a mixture of one part of tenth

normal potassium chlorid and two and a half parts of tenth normal sodium chlorid as a standard; and the comparative contraction of the melanophores as the index of the strength of posterior lobe extracts. The method has not yet been tested sufficiently to allow any conclusion as to its general availability.

Pharmacodynamic Effects of Posterior Lobe Extracts.—Extracts of the posterior lobe of the hypophysis usually stimulate smooth muscle to contraction. Magnus and Schäfer (1901-02) first observed that a diminu-

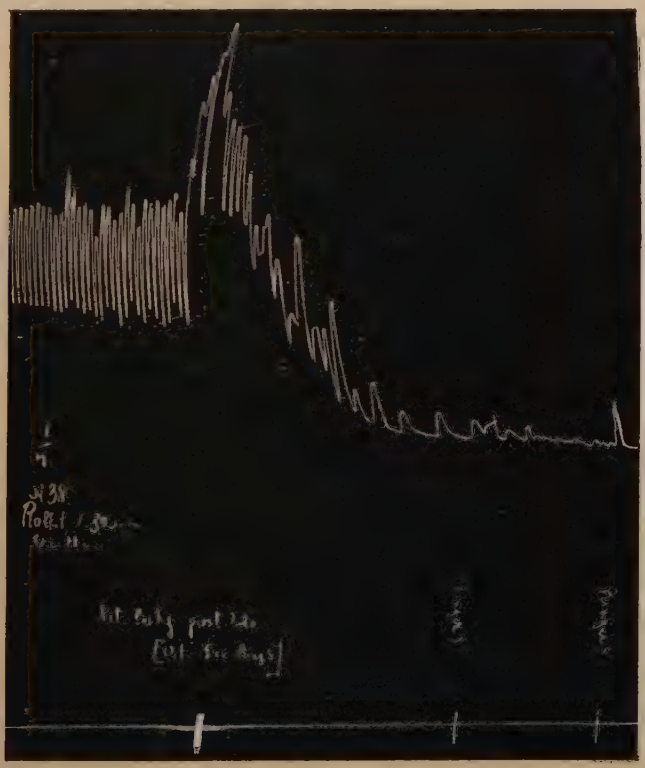


Fig. 5. The constrictor and the relaxing effect on the isolated loop of the intestine of a posterior lobe preparation. (After Shamoff, Am. J. Physiol.)

tion of splenic volume occurred after their injection, this was confirmed by Dale(*b*) (1909); and Frankl-Hochwart and Fröhlich (1910) reported that the bladder was similarly affected. Although Dale and Laidlaw (1912-13) failed to obtain such an effect Hoffman (1912) confirmed the earlier observations in demonstrating that the reaction occurred after intraspinal injections of the extract thus demonstrating its absorption from the canal and indirectly supporting Cow(*a*) (1914-15) in the idea that the normal path of the hypophyseal secretion to the organism is by this route. Nevertheless, since Carlson and Martin (1911) and Jacobson

(1920) have shown that the cerebrospinal fluid does not normally exhibit any of the activities of posterior lobe extracts the hypothesis is of doubtful value. Waddell(*a*)(*b*)(*c*)(*d*) (1916-17) tested the activity of the drug on a wide variety of smooth muscle tissues and found that while the uterus masculinus of the rabbit and isolated strips of the vagina were stimulated to contraction, a depressor effect was obtained with the frog esophagus and no effect at all with the quiescent vas deferens.

Effects on Intestine. The studies of Ott and Scott(*c*) (1911), Meoni (1913) and Shamoff (1915-16) indicated that the action of posterior lobe extracts on the intestinal musculature was also that of constriction. Nevertheless, Parisot and Mathieu(*a*)(*b*) (1914) noticed that an inhibitory reaction and relaxation occasionally occurred and Hoskins (1916) called attention to the fact that this depression of intestinal tone and peristalsis on intravenous injection occurred not infrequently and that the test of this activity should be made on all commercial products, inasmuch as they are occasionally used to stimulate intestinal tone. Pancoast and Hopkins (1917) made a careful study, using the X-ray, of the action of the extracts on movements of the alimentary tract and found that a primary inhibition of the stomach occurred which was followed by a secondary augmentation of activity, with a delayed or negative reaction of the small and large intestine. Recently Zondek (1920) ingeniously fashioned a little celluloid window in the abdominal wall of his experimental animals and got a first-hand view of the processes taking place after the injection of the extracts. He also found that a preliminary inhibition occurred that, however, was followed by an evident stimulatory period in which peristalsis was increased. He is of the opinion that the hypophyseal secretion exerts a regulatory effect on peristalsis. The studies of Santi (1914) of the comparative stimulative effect of extracts of posterior lobes from pregnant and nonpregnant animals led him to the conclusion that the former were more active.

Effects on Uterus. Dale(*a*) (1906) was the first to record that pituitary extracts exert a constrictor action on the uterine musculature. This was confirmed by Bell and Hick (1907), Führer (1913), Itagaki (1917) and many others. Although Bell and Hick (1907) observed that the resting uterus of the rabbit did not respond to the application of posterior lobe extracts, this has not been found to occur with the uteri from other mammals. Lieb (1914-15) and Charteris (1917) have shown that the surviving human uterus reacts by a contraction whether pregnancy has begun or not. Cow (1919) has confirmed this and made the further observation that a relaxation may occur at times instead of a contraction. He is of the opinion that the point of attack of the drug is the peripheral nervous system and not the end organ.

Effects on Circulation. From an historical point of view the discovery by Howell(*b*) (1898) that the pressor effect of hypophyseal extracts

is due to some constituent of the posterior lobe, was the beginning of the mass of studies that have been made of this portion of the hypophysis. This investigator observed that when saline or glycerin extracts of the posterior lobe were intravenously injected into dogs there occurred within a few minutes a rise of blood-pressure which was quickly followed by a fall. During this period the heart beat was somewhat slower and apparently more feeble. The fall in blood-pressure lasted but a short time and then rose again usually above the level obtained immediately succeeding the injection. This second rise in pressure was accompanied by a very marked slowing of the pulse rate that lasted for a long time and was slowest at about the same time the pressure was at a maximum. When the injections were made subcutaneously no distinct effect could be de-

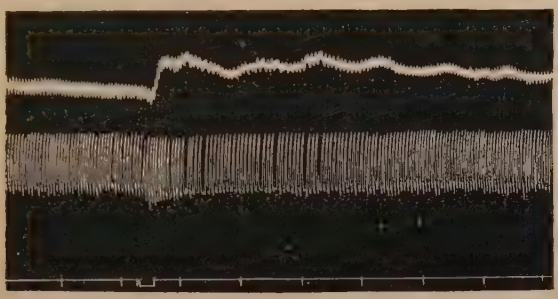


Fig. 6. Tracings which demonstrate the effect of the administration of 0.9 c.c. of a 1:25 dilution of posterior lobe extract on the blood pressure and respiratory movements. The upper curve shows the pressor effect and the middle curve records the movements of the diaphragm. Time is in half minutes. (After Nice, Rock & Cortright, Am. J. Physiol.)

tected on the heart or blood vessels from which observation it appeared as if the active pressor substance of these extracts is destroyed or neutralized in some way by the organism so that its effect is but temporary. Howell also was inclined to believe that the heart and blood vessels become less susceptible to subsequent injections since when these are given the circulatory response is less marked or negligible. This immunity to repeated injections cannot be attributed to a paralysis of the musculature of the vascular system or their nerves, since no decrease of vascular tone is observed. From the fact that the rise in pressure is more marked after the vagi have been cut and also occurs after section and extirpation of the cord below the medulla, Howell is of the opinion that the pressor effect is probably mediated through the action of the substance in the extract on the peripheral arteries and not through the central nervous system. Schäfer and Vincent (1899) confirmed Howell's observation that the pressor principle is confined to the extracts of the posterior lobe and that immunity is exhibited to the effects of repeated injections. From then on down to the present the studies of Magnus and Schäfer (1901-02) and others have demonstrated conclusively that the characteristic

pressor response is due to a substance contained in the posterior lobe of the hypophysis and its extracts. It should be noted that the type of pressure increase produced by posterior lobe extracts is different from that observed after the administration of epinephrin in that it is maintained at a high level for a much longer period of time as demonstrated by Mummery and Symes (1908) and Bell and Hick (1909).

The question as to whether or not the point of attack of the effective substance is the peripheral mechanism, the central nervous system or the heart itself is still an open question with the evidence tending towards the broader view of Wiggers (1911) that all are involved. He considers that the slowing of the heart occurring synchronously with the rise in blood-pressure is an indication of the stimulation of the cardio-inhibitory center. Werschinin (1913), Tigerstedt and Airila (1913), Claude, Porak and Routier(*a*)(*b*) (1913), Wiggers (1911), Airila (1914) and others, present evidence from various angles which effectively support Howell (1898) and Schäfer and Vincent (1899) in the opinion that there does occur a generalized constriction of the peripheral arterioles. Nevertheless, Fröhlich and Pick(*b*) (1913) and Hallion (1914) have reported experiments which tend to show that on certain parts of the vascular system, such as the pulmonary artery, there may be produced a hypotensive instead of a hypertensive effect. The lower cardiac activity, combined with the lesser amount of blood in the peripheral vessels, led Claude and Porak(*a*)(*b*) (1913) to the opinion that the action was a selective toxic one on the myocardium. Werschinin (1913), Tigerstedt and Airila (1913), Wiggers (1911) and others seem to coincide in this opinion as far as the second phase of the reaction is concerned. This belief is supported by the observations of Etienne and Parisot (1908) and Hofstätter (1919) who found that repeated injections of posterior lobe extracts resulted in cardiac hypertrophy, while Bauer and Aschner (1919) were unable to demonstrate that the permeability of the blood vessels themselves was affected. That the pressor action is mediated by a specific substance contained in the extracts and is not dependent upon any secondary reaction induced through the liberation of epinephrin from the adrenals, as indicated from the studies of Porak (1913), is shown by the fact that Hoskins and McPeek (1913-14) obtained the characteristic rise of blood-pressure on injection of posterior lobe extracts when the adrenal veins were occluded. Hecht and Nadel (1913) made a preliminary study of the phenomenon using the electrocardiograph but their results were not sufficiently numerous to allow any definite conclusions to be drawn therefrom. Whether the primary point of attack of the pressor substance is the neural mechanism or the muscular mechanism of the vascular system is as yet undetermined. The initial tachycardia observed by Claude, Porak and Routier (1913) and the hypertrophy induced by repeated injections as described by Hofstätter (1919) could as well be indicative of a neural stimulation as of a muscle

effect. From the fact that Howell (1898) got an augmented pressor effect with the vagi cut and the negative findings of Bauer and Aschner (1919) with regard to permeability changes of the blood-vessels one might be led to the opinion that the initial mechanism stimulated was neural. The fact that most of the reactions to pituitary extract are such as follow sympathetic stimulation whereas the predominant effect in the intestine is such as results from vagus stimulation offers an obvious obstacle to the assumptions of any selective nervous stimulation. In view of the present undeterminate status of the problem any decisive conclusion is unwarranted.

That there is also a depressor substance in extracts from the posterior lobe was first demonstrated by Schäfer and Vincent (1899). This substance they were able to separate in solution from the pressor substance by virtue of the fact that it is soluble in saline solution and absolute alcohol whereas the pressor substance is insoluble in absolute alcohol. This observation was confirmed by Magnus and Schäfer (1901-1902). Führer (1914) in his extensive studies of preparations of pure active materials from the posterior lobe was also able to obtain a mixture that caused depressor effects when injected into experimental animals as was Claude and Porak (1914). However, under ordinary conditions of preparation the pressor substance is normally present in such amounts as to mask the effect of any depressor compound that may or may not be also contained in the extracts. Kleemann (1913) made a comparative study of the effects on the circulation of extracts of the posterior lobes from castrated, pregnant and normal animals. He found that the extracts from the castrated subjects gave the same type of reaction as did those from the normal animals, but that vasodilatation as well as vasoconstriction resulted from the hypophyseal extracts from the pregnant animals.

According to Parisot and Mathieu(*c*) (1920) the extracts have two opposite actions according to the size of the dose used. The dynamogenic doses producing positive responses are small and the effects are produced under conditions that might occur in the living organism. The antidynamic effects are those that are produced by the larger doses, they tend to be depressor effects and are presumably not evoked in the living organism. Such a suggestion is valid on the basis of many of the data at hand. Nevertheless, it is possible that the opposite effects obtained not only on blood-pressure but also on renal and smooth muscle tissue activity are due to differences in the previous condition of neural tone of the experimental subject. This is a phase that has as yet lacked the recognition it deserves but has been shown by Hatai and Hammett (1920) and by Hammett (1920-21) to be an important factor in the type of response elicited by various experimental procedures.

An additional possibility lies in the evidence that is accruing to indicate that the secretion of the anterior lobe is the precursor of alleged

specific active principles of the posterior lobe. Hamburger(*a*)(*b*) (1910) has shown that anterior lobe extracts are depressor in action and it may be that the posterior lobe extracts exhibiting a depressor effect contain a preponderance of the untransformed depressor precursor of the pressor principle. Such a hypothesis of the derivation of the various effective substances of posterior lobe extracts from one compound would not negate the production of specifically acting compounds representing either different types or different degrees of transformation of the original mother substance.

Effects on Kidneys. The response of kidney function to the administration of extracts of the posterior lobe of the hypophysis is of great pharmacological and therapeutic importance. From the records of the reported experiments it appears as if two apparently opposed sets of reactions may occur and as yet no definite indication of the factors underlying the differences in response is evident. That such extracts induce an increased kidney activity as expressed in an increased flow of urine has been demonstrated by Magnus and Schäfer (1901-02), Schäfer and Herring (1906), Thaon(*c*) (1910), King and Stoland (1913-14), Hoskins and Means (1912-13) and others. Not only have diuretic effects been obtained but antidiuresis has also been shown to occur as a result of injections of these extracts. Pentimalli and Quercia (1912), Frey and Kumpiess (1913-14), Garnier and Schulman(*a*)(*b*) (1914), Von Meyenberg (1916), Motzfeldt(*a*)(*b*) (1916) and Rees (1918) have obtained a diminution of urinary output under such conditions. The only present indication of a possible cause of these differences in results lies in the apparently unnoticed observations of Magnus and Schäfer (1901-02) that when they injected the depressor compound as separated from the hypophyseal extracts by Schäfer and Vincent (1899) a restriction of urinary flow was obtained instead of a diuresis. A study of the literature also reveals the fact that the greater number of those workers reporting a diuretic effect administered the extracts by the intravenous route, while those who reported an antidiuretic effect administered the drug by subcutaneous or intramuscular injections. It may hence be possible that the latter mode of giving the extract results in the destruction of the pressor and diuresis producing substances while the depressor and antidiuretic compounds are more resistant and hence effective.

The question of the nature of the action of the posterior lobe extracts when diuresis is produced has aroused some considerable controversy. The earlier investigators, Magnus and Schäfer (1901-02) and Schäfer and Herring (1906) were inclined to attribute the effect to a direct stimulative action of the drug on the renal epithelium. This conception is supported by the studies of Hoskins and Means (1912-13) who showed that no constant relation existed between pulse pressure, systolic pressure and the diuresis, and that the most common condition accompanying

diuresis was an augmented systolic pressure with a decreased pulse pressure. Nevertheless, neither they nor Schäfer and Herring (1906) deny the possibility that the diuresis may not be due to an increased blood supply to the kidney. Houghton and Merrill (1908), having observed a vasoconstriction of the renal vessels as a result of the injection of posterior lobe extracts, expressed the opinion that the diuresis was due to an increased blood-pressure following the generalized vasoconstriction obtaining under the experimental conditions. This opinion was apparently supported by the studies of Dale (1909) and Pal (1909) who also found that these extracts caused constrictions of the renal epithelium. Thaon(*c*) (1910) concluded from his experiments that the increased blood-pressure

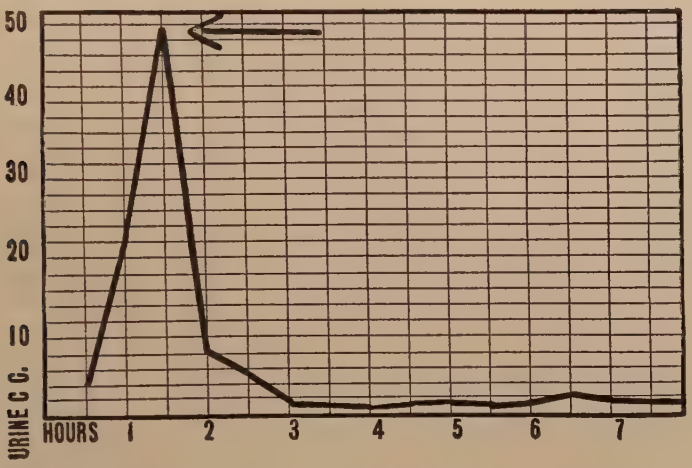


Fig. 7. A diagram showing the antidiuretic action of 2 c.c. of pituitrin intravenously injected into a rabbit in which artificial polyuria had been induced by copious water administration. (After Motzfeldt., J. Exper. Med.)

is probably the main factor concerned in the diuresis but that a toxic effect of the extract on the renal epithelium is also involved because he obtained renal hyperemia and hematuria as a result of long continued injections. Nevertheless, King and Stoland (1913-14) observed that diuresis occurred only as the kidney dilated, and Knowlton and Silverman (1918) failed to find any increased oxygen consumption by the kidney after injection of posterior lobe extracts and hence came to the conclusion that the diuretic response is satisfactorily explained on the basis of vascular changes, such as an increased blood flow and pressure or a vasodilatation of the renal vessels.

Motzfeldt(*b*) (1917) made a very careful study of the antidiuretic effect of posterior lobe extracts utilizing various methods of administration and found in all cases a restriction of diuresis artificially induced by the ingestion of large amounts of water. From the fact that this antidiuretic effect was inhibited by section of the splanchnic nerves he concluded that

the mechanism is integrated through the sympathetic nervous system and that the renal vasomotor system is of prime importance. This correlation of the effects of these extracts on the kidneys with the neural control is also supported by the studies of Addis, Shevky and Bevier (1918). Addis (1918) and his coworkers have shown that the injection of posterior lobe extracts depresses the excretion of urea, even on high levels of blood-urea content, and that this action tends to counteract the stimulating effect of epinephrin on urea excretion to the extent that by suitable combinations of the two drugs no changes are obtained. They consider that the products of the activity of the hypophysis and the adrenals may exert a balancing effect on the excretory functions of the kidney as controlled through the nervous system.

Effects on Respiration. The influence of injections of posterior lobe extracts upon respiration were first noted by Mummery and Symes (1908) and Houghton and Merrill (1908), the former having recorded a diminution in amplitude of the respiratory movements and the latter an increase in their number. Nice, Rock and Courtright (1914) made a careful study of the exact changes induced and came to the conclusion that the first effect is an increase in the depth of the respirations which is followed by shallowness and a decrease in rate, although sometimes an increase may be obtained. The onset of the phenomena is synchronous with the circulatory changes, but the duration is less. An immunity to further injections is produced. Fröhlich and Pick(*a*) (1913) noted symptoms which they attributed to bronchial spasms. The respiratory effects in their experimental animals consisted of deep inspirations followed by shallow and apparently fruitless expirations. The nature of the action of the stimulating substance of the extracts was stated by Trendelenburg (1912) not to be that of a bronchoconstrictor. Nevertheless, the later experiments of Houssay (1918) and others indicate that the effect is actually a constriction of bronchial musculature. The point of attack of the bronchoconstricting substance has been attributed by Fröhlich(*b*) (1914) to the vagal endings in the bronchial musculature which have been sensitized by the drug. In connection with this opinion the findings of de Bomis and Susanna (1909) that infundibular extracts induce a constriction of the pulmonary arteries is interesting. Aside from these few statements but little valid information concerning the action of posterior lobe extracts on respiration is available.

Effects of Posterior Lobe on Metabolism.—Studies of the effects on metabolism of the administration of posterior lobe preparations are few and unsatisfactory. Malcolm (1904) reported that he obtained nitrogen retention, a preliminary increase in phosphorus excretion followed by retention, and increased calcium output, which led him to conclude that the posterior lobe exerted a catabolic influence on bone. This conclusion is supported by the observation of Franchini (1910) of a decrease in the

calcium and magnesium content of the blood after posterior lobe administration. Aldrich(*b*) (1912-13) found no changes from the normal in the growth of his rats that had been fed posterior lobe substance. Frey and Kumpiess (1913-14) in a study of the effect of pituitary extracts on urinary output got a constant per cent phosphorus excretion, which when taken with the diuresis produced would tend to show a phosphaturia. The nitrogen elimination was variable while the uric acid ran parallel to the amount of urine voided. Farini and Ceccaroni(*b*) (1913) obtained an increased hippuric acid excretion as the result of posterior lobe injections and Hewitt(*b*) (1914) reported that the administration of small amounts of the substance together with 0.25 gram thyroid resulted in an increased ammonia output over that excreted on the thyroid substance alone. Although these experiments (either singly or as a whole) are unsatisfactory in that they fail to give any but a patchwork picture of the metabolic changes induced by the hypophyseal extracts, they do show that the administration of such preparations is not unattended with deep-seated metabolic disturbances. This is particularly true of long-continued administration as shown by Schäfer and Vincent (1899) and Thaon (1907).

The metabolic processes concerned in sugar mobilization and utilization are considered by some to be specifically influenced by the posterior lobe. Cushing (1912) and Bell (1919) report the appearance of glycosuria after operations on the pituitary as evidence of a probable influence of the hypophysis on carbohydrate metabolism. Such evidence is not convincing when we consider that most operative procedures, and particularly those associated with manipulations at the base of the brain, usually give rise to a more or less extensive sugar excretion. A similar objection applies to the recent work of Keeton and Becht (1919) in which glycosuria was obtained as a result of stimulation of the hypophysis. On the other hand the experiments of Weed, Cushing and Jacobson (1913) have shown that the stimulation of the superior cervical ganglion produces glycosuria in the rabbit, cat or dog, even if all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks or cervical cord are excluded, while if the posterior pituitary has been previously removed the ganglionic stimulation does not result in glycosuria. With regard to the effects of actual injections of posterior lobe extracts Goetsch, Cushing and Jacobson (1911) obtained glycosuria as a result of such procedure and Achard, Ribot and Binet (1919) found that the hyperglycemia induced by intravenous glucose injections was enhanced by the simultaneous injection of posterior lobe extract and that such an extract given alone also cause hyperglycemia. Franchini (1910) also noted the occasional occurrence of glycosuria in rabbits as a result of similar manipulations. Quadri (1914) studied the effect of posterior lobe extracts on alimentary glycosuria and it is a well known clinical fact that an increased sugar tolerance often accompanies hypopituitarism.

These positive observations would tend to support Cushing's (1912) opinion that the posterior lobe of the hypophysis has a glycogenolytic function. Kojima's (1911) report is interesting in this connection from the fact that he obtained changes in the pancreas as the result of feeding pituitary. On histological examination of the pancreas of the experimental animals he found that many of the cells of that tissue had undergone vacuolization; that there was an edema of the entire organ, excepting the isles of Langerhans, and that these were crowded with granules.

Effects on Secretions and Lactation.—Turning now to a brief presentation of the effect on other secretory functions it is found that both Rogers (1915-16) and his collaborators and Pal (1916) have obtained an inhibition of the flow of gastric juice as a result of the administration of posterior lobe extracts, and Wiggers (1911) reports a similar inhibition of pancreatic secretion. Solem and Lommen (1915) found that the drug caused a diminution of the flow of saliva and also of the blood through the salivary glands. Since the retardation of the salivary flow was greater than that of the circulation through the gland they concluded that the extract inhibits the action of the secretory nerves to the gland as well as causes vasoconstriction.

The stimulating effect of posterior lobe extracts on the lactating mammary gland was first observed by Ott and Scott(*a*)(*b*) (1910) and confirmed by MacKenzie (1911), Schäfer and MacKenzie (1911), Houssay and Maag (1914) and others. This was shown to be a common reaction in many types of mammals by Simpson and Hill (1914-15), Hill and Simpson(*a*)(*b*)(*c*) (1913-14), Hughes (1915) and others. Hofstätter (1919) claims that the long continued administration of posterior lobe extract causes a development of the mammary glands; Bell (1919) was unable to show definitely such developments in virgin animals. The stimulative effect on lactation is rapid but transitory in nature. The milk expressed at the time is usually of a greater fat content than normal though this is denied by McCanlish (1918). There is a tendency to a lessened milk secretion the day after the effect of the extract has been tested. Hammond (1913) is of the opinion that the increased milk flow is a true secretory phenomenon and not due to any rise in blood-pressure, basing his opinion on the higher fat content of the milk. Maxwell and Rothera (1915) agree with the idea of the secretory nature of the stimulus. Schäfer(*c*) (1915) opposes this conception and considers that the effect is not a true secretory stimulation but is a simple squeezing out of the milk by the contraction of the muscles of the alveoli and ducts. This opinion is supported by the observations of Gaines(*a*)(*b*) (1914-15), who has found that the flow depends on the amount of milk in the gland and that the reaction can be obtained from the excised gland. He is accordingly of the belief that the action is not a true secretory stimulation, but is merely the constrictor

effect on the smooth musculature of the gland. With this Bell(*b*) (1919) is inclined to agree.

The studies of the comparative action of posterior lobe extract with other drugs have been many, but those concerned with ergotoxin and epinephrin are of greatest interest. Fröhlich and Pick(*b*) (1913) observed that posterior lobe extracts exerted an antagonistic action on the effects produced by ergotoxin and this was confirmed by Cow (1919). Dale (1909) concluded from his studies that epinephrin and the effective principles of posterior lobe extracts are two different substances. Houssay (*e*) (1915-16), Cow(*c*) (1919) and others have adduced evidence supporting this idea, the former considering that the activity of epinephrin is antagonistic and never synergistic to that of posterior lobe extracts. This is supported by the observations of Githens and Meltzer (1916).

The Pathological Anatomy and Histology of the Hypophysis ..... *J. P. Simonds*

Introduction—Malformations of the Hypophysis—Mechanical Injury—Changes Incident to Age—Circulatory Disturbances—Necrosis and Calcification—Degenerations—Pigmentation—Changes in Infectious Diseases—Alterations Associated with Changes in the Thyroid Gland—Inflammation—Pyogenic Infections—Syphilis—Tuberculosis—Actinomycosis—Miscellaneous Lesions—Aplasia, Hypoplasia and Atrophy—Tumors—Hyperplasias—Cysts—Animal Parasites.

The Pathological Anatomy and Histology of the Hypophysis

J. P. SIMONDS

CHICAGO

Introduction

A systematic description of the morbid anatomy and histopathology of the hypophysis must take into account the apparently normal variations in the weight and size of the gland and the uncertainty which still exists as to its normal histology. The recorded average weights of hypophyses of adults said to be normal have varied from 0.5 to 0.807 gram. The following table illustrates the variations in the reported average weights of the gland:

	Both Sexes	Males	Females
Vierordt	0.50 g.		
Schoenemann	0.63 g.		
Boyce and Beadles		0.453 g.	0.60 g.
Simmonds		0.737 g.	0.807 g.
Tölken	0.54 g.		
Erdheim	0.612 g.		
Munson and Shaw	0.545 g.		

One source of error in determining the weight of the normal hypophysis has been pointed out by Tölken, namely, that account has not been taken of the effect of pregnancy, especially of repeated pregnancies, upon the weight of the gland. The figures given by Erdheim and by Tölken are the averages of the weights of 34 and 98 hypophyses, respectively, from males and virgin females, and may perhaps be accepted as reasonably accurate. The average weight of the hypophyses of women who have borne children will be somewhat higher than the weight of this gland in males of the corresponding age period.

The average sizes of the hypophysis have been stated as follows:

	DIAMETER IN MILLIMETERS		
	Transverse	Sagittal	Vertical
Zander	11.9	8.0	6.55
Schoenemann	12.5-18.0	5-6	
Thom	12.11	6.83	5.11
Erdheim	14.4	11.5	5.5
Tölken	14.2	10.0	5.9
Munson and Shaw	14.1	10.5	5.6

In the above table the average transverse and vertical diameters do not show any very marked variation. The sagittal diameters, however, range from 5 to 11.5 mm. In a small series of apparently normal glands which I have measured, the higher figure appears to be more nearly correct.

The size and weight of the hypophysis are influenced not only by the pathologic processes to which it is subject, but also by age, by pregnancy and castration, and by changes in other glands of internal secretion. These variations will be considered in their proper place.

The anatomical location of the hypophysis has an important bearing upon certain features of its pathology. It is inclosed by rigid, unyielding bone in front, below and behind; above, it is covered with the dense dura mater; while laterally it meets the pressure from the internal carotid arteries. Any enlargement of the hypophysis shows itself first in the transverse and vertical diameters, and is manifested by a bulging of the dura mater covering the sella turcica. LeCount has suggested that if the sella becomes enlarged primarily as a result of the overgrowth of the bones of the base of the skull, the hypophysis may become secondarily enlarged by a process of edema *ex vacuo*.

Lesions of the hypophysis may be primary in the gland itself; or they may be secondary to pathologic changes in other glands of internal secretion, or to extra-hypophyseal pathologic processes within the cranial cavity.

The "factor of safety" of the hypophysis appears to be large. In many cases of tuberculosis, syphilis and embolic processes in the gland, a large part of the hypophysis has been destroyed without the occurrence of symptoms recognized to be due to hypopituitarism. Such cases have been recorded by Simmonds(*g*)(*i*), Merkel, and others.

Malformations of the Hypophysis

The hypophysis is derived from two widely separated sources, and its embryologic development is a complicated process. It is not surprising that congenital malformations are not uncommon. Rippmann, Jakoby, and Boyce and Beadles(*b*) have reported cases of absence of the hypophysis. Bland-Sutton mentions, without giving details, a double hypophysis in a

foal. Each hypophysis had its own sella turcica. Ahlfeld saw a double hypophysis in a human infant.

Congenital displacements of the hypophysis are more common than its absence or its reduplication. Spring, Klinkosch, and Exner each observed the hypophysis in the sac of an encephalocele which projected either through a patent craniopharyngeal canal or through a cleft (Exner) in the base of the skull. In a pig embryo Jakoby found the hypophysis in contact with the roof of the pharynx. Suchanek and Haberfeld(*b*) have each reported a case in which the hypophysis was found wedged into a patent craniopharyngeal canal with its upper end at the floor of the sella turcica, and its lower end projecting into the roof of the pharynx. The shape of the gland was greatly distorted. Lawson found a "struma of the hypophysis" growing through a defect in the sphenoid bone. In three cats Haberfeld(*a*) found patent craniopharyngeal canals containing hypophyseal tissue, but with similar tissue also in the normal position in the sella. Rössle has reported a case of dystrophia adiposogenitalis in which the infundibulum was absent.

Accessory hypophyses in the form of rests are common. Haberfeld(*a*), Christeller, Pende(*a*), and Civalleri found these quite constantly in human subjects. They are present in the mucous membrane of the vault of the pharynx and along the front surface of the infundibulum. Their physiological significance is disputed. They are important, however, because they may give rise to tumors.

Acquired malformations of the hypophysis are not uncommon. Total, or almost total, absence of one or both lobes, due to some pathologic process, has been recorded by Boyce and Beadles(*b*), Simmonds(*h*), Bleibtreu, Fraenkel(*b*), and Ponfick(*a*). Changes in the shape of the hypophysis may result from various causes. When it is hypertrophied, as in pregnancy, it is more plump and Simmonds(*e*) has described it as shaped like a "full sausage." In old age, the pit which is normally present on its upper surface is deepened, and the gland becomes somewhat trough-shaped. In cases of pressure upon the hypophysis by hydrocephalus and by tumors of its infundibulum or in the floor of the third ventricle of the brain, it becomes flattened and scaphoid. When the carotid arteries are tortuous, dilated and partially calcified, the hypophysis may become faceted on its lateral surfaces. Kümmel and Rheinhardt found the hypophysis displaced, compressed and flattened by pressure from aneurysm of one of the vessels of the circle of Willis.

Mechanical Injury

Trauma.—The hypophysis may be injured in trauma of the skull. Schmorl observed hemorrhagic necrosis of the hypophysis in a case of fracture of the base of the skull. Simmonds(*f*) has "frequently seen hem-

orrhage into the hypophysis in traumas of the skull." In my own series of cases, which includes a number of cases of fracture of the base of the skull, I have observed hemorrhage into the capsule of the hypophysis, but not into the substance of the gland itself. The clinical features of cases of hypopituitarism following injury to the skull have been reported by Madelung, Cushing(*b*) and Stolper. The latter's patient ultimately came to autopsy which revealed a struma of the hypophysis. Bleibtreu has recorded a case in which gigantism and acromegaly developed after a severe trauma to the head. Four years later, at autopsy the sella turcica was found occupied by a mass of mature connective tissue with a few minute remains of the anterior lobe.

LeCount and Apfelbach have shown that linear fractures of the base of the skull follow fairly definite lines. They do not mention the relative frequency with which these lines involve the sella turcica. In 34 cases of fracture of the base of the skull in which I have accurate measurements and charts, the line of breaking crossed the sella 5 times. In these cases the fractures either ran almost in the coronal plane, passing between the spheno-maxillary fissure in front and the foramen ovale and foramen jugularis behind, and thence transversely across the sella; or, more rarely, the line of fracture extended along the sagittal plane and crossed the sella in an antero-posterior direction. The anatomical relations of the sella turcica and their influence upon the course of fractures of the base of the skull may account for the relative infrequency of injury to the hypophysis in traumas of the head.

Injuries of the hypophysis due to intracranial pressure.—The effect of pressure by tumors and internal hydrocephalus upon the hypophysis has been referred to. More important than the anatomical malformations which they induce is the effect upon the function of the gland. Cushing(*b*) and Stumpf(*b*) are of the opinion that at least a part of the secretion of the hypophysis is absorbed through the infundibulum. Pressure which interrupts these channels of absorption may be the etiologic factor in some cases of hypopituitarism.

Changes in the Hypophysis Incident to Age

Changes that are more or less physiological occur in the hypophysis with advancing age. In the first place, its size and weight diminish. According to Simmonds'(*e*) figures, based upon the weights of 800 hypophyses, the weight increases up to the age of 60, and then gradually diminishes. Thom found the average size for both sexes to be greatest between 40 and 50. After that age the hypophysis became smaller, the diminution affecting the vertical diameter more than the transverse and sagittal diameters. This is due largely to an increase of fibrous tissue in

the gland, which, upon contracting, flattens the hypophysis and causes a deepening of the pit normally present upon its upper surface.

Schoenemann found fewer strictly normal hypophyses with advancing age, as shown in the following table:

Age	Normal	Abnormal	Per cent Abnormal	Total
Newborn	8	3	27%	11
1 to 20	7	7	50%	14
20 " 40	8	20	71%	28
40 " 60	4	35	90%	39
Over 60	0	19	100%	19
Totals	27	84		111

The chromophile cells, which predominate in middle life, become fewer in number in old age (Erdheim(*a*)). Fat droplets begin to make their appearance in the cells of the anterior lobe in early infancy. These droplets increase in number and size with advancing age, so that in old age they may be as large as the nuclei themselves (Erdheim(*a*)). They appear to be largest and most numerous in the basophil cells. Kraus(*a*) found an increase in the size and number of the droplets of isotropic lipoidal substances in the cells of the anterior lobe in old age. He considered these not as secretion products, but as an expression of depressed cell function.

Fig. 1. Growth of cells of the pars intermedia into the pars posterior of the hypophysis. Magnified 70 times. A small part of the anterior lobe is shown in the lower right hand segment.

There appears to be a tendency with advancing age for the cells of the anterior lobe to grow backward into the posterior lobe. Erdheim(*a*) observed it in three individuals, 50, 53 and 73 years old, respectively. This condition is illustrated in Fig. 1, which is a photomicrograph of a section of the hypophysis of a colored man about 60 years old. Tölken observed this process in 50 out of 105 hypophyses examined.

Circumscribed adenomatous growths within the anterior lobe are common after the age of 40, as observed by Löwenstein, Kraus(*b*), and

others. This tendency to the development of adenomas in old age is in harmony with Goodpasture's conception, that as individuals grow old many cells by dedifferentiation—i. e., by the "elimination of structural differences"—free themselves of the more rigid demands of functional specificity and become capable of growth.

Circulatory Disturbances

Hemorrhage.—Hemorrhage into the hypophysis may occur from various causes. Strauch observed subcapsular hemorrhages in a case of internal hydrocephalus. Simmonds(*f*) and Schmorl have seen hemorrhage into the hypophysis as a result of trauma. In several cases of fracture of the base of the skull I have found hemorrhage into the capsule of the hypophysis but not into the substance of the gland itself. Hunter(*b*) and the author found hemorrhage into the pituitary body in cases of apoplexy. In my case, about one-third of the posterior lobe was densely infiltrated with blood. Hemorrhage into the anterior lobe following thrombosis of a blood vessel of the hypophysis has been described by Merkel and Berblinger(*c*). In the posterior lobe of a 60-year-old man who died of hemorrhagic (lethargic) encephalitis, I found numerous, minute hemorrhages into the substance of the posterior lobe. Hemorrhages into the hypophysis are frequently agonal. Luzzatto and Lubarsch found hematogenous pigment, the remains of an old hemorrhage, in the neurohypophysis. Hemorrhage into tumors of the hypophysis are common; extensive extravasations of blood into neoplasms having been recorded by Bailey, Eppinger, Eisenlohr, Anders and Cattell, and Michel.

Hyperemia.—In the examination of a large series of hypophyses, one is impressed by the very great variation in the amount of blood present in the anterior lobe in different specimens. The blood vessels of the hypophysis are thin-walled and are capable of easy dilatation. Passive hyperemia of the hypophysis may be caused by any condition which induces an overfilling of the intracranial veins and sinuses, such as pressure by tumors upon the veins of the neck, valvular disease of the heart, etc. Strauch noted "excessive hyperemia" of the anterior lobe in a 9-year-old girl suffering from hydrocephalus.

Abramow found hyperemia of the anterior lobe of the hypophysis as a constant change in experimental diphtheria in guinea pigs. In 22 out of 62 hypophyses examined by Thom there was dilatation, and sometimes an increase in the number, of the blood vessels, associated with a variety of pathological lesions in other parts of the body. The most pronounced hyperemia in my series of hypophysis was in one form a man who died from hemorrhagic (lethargic) encephalitis.

Edema.—Edema of the hypophysis is not easily detected because of the slight amount of connective tissue of the anterior lobe and because of the normal looseness of the structure of the neurohypophysis. Thaon(*b*) asserts that the hypophysis has no lymph vessels. If this be true, it is possible that edema of the hypophysis does not occur.

Thrombosis.—The formation of thrombi in the vessels of the hypophysis is of relatively rare occurrence. In many of the wide vessels of the anterior lobe, one frequently sees bluish or pink staining masses of homogeneous material, with or without accompanying red blood cells. These appear to be intravascular colloid. In one of my specimens, however, there were three small vessels in one part of the anterior lobe which contained purplish masses showing a filamentous network like fibrin, the whole mass closely resembling a thrombus. There were no changes in the adjacent cells. Merkel has observed a thrombus in a vessel of the anterior lobe due to an embolus of metastatic tumor cells. Simmonds(*g*) has also observed thrombosis in the vessels of the hypophysis.

Embolism and Infarction.—Benda(*b*)(*c*) has made a careful study of the blood supply of the human hypophysis. The gland is supplied with blood from three paired sources. One pair of vessels, previously described by Luschka, passes from the internal carotid artery to the infundibulum, and, turning downward, probably supplies the pars intermedia. A second branch, on each side, leaves the internal carotid artery at its entrance into the sinus cavernosus; this small vessel goes to the groove between the two lobes and enters the anterior lobe at about the middle of its postero-lateral border. There are also fine branches from the pia mater to each side of the infundibulum. These findings of Benda have been confirmed by Simmonds(*g*) and Schmorl. The blood supply of the human hypophysis appears to differ from that of the dog as described by Dandy and Goetsch.

The arteries which supply the anterior lobe of the hypophysis differ from those which go to the neurohypophysis in this important respect, that they are functional end-arteries while those that supply the posterior lobe anastomose freely. Hence, emboli which lodge in branches to the anterior lobe cause infarcts, while those which are stopped in vessels of the posterior lobe are without effect, unless they contain bacteria or tumor cells. In such event an abscess or a metastatic tumor develops in the neurohypophysis. In more or less complete infarction of the anterior lobe of the hypophysis the infundibulum and pars intermedia may remain intact because they receive a separate blood supply through blood vessels which run upon and in the infundibulum from the pia mater.

Embolism and infarction in the hypophysis are not uncommon occurrences. Simmonds(*f*) found embolic processes 20 times in 1,500 hypophyses, from all sources, examined. Infarcts of the anterior lobe have also been observed by Merkel, Schmorl, Schmidtmann, Benda(*c*), Berblinger(*c*),

and Glinski. They are usually anemic infarcts; but Merkel and Berblinger(*c*) have each reported instances of hemorrhagic infarcts of the hypophysis. In both of these cases, the infarction was due to thrombosis of a vein and not to an embolus in an artery.

In a detailed study of embolic processes in the hypophysis Simmonds(*g*) reported 4 cases of mycotic emboli in the neurohypophysis, with small localized abscesses; 2 cases of mycotic emboli in the anterior lobe; and 4 cases of typical anemic infarcts of the anterior lobe. Of these 10 hypophyses, 9 were from persons dead from streptococcic or staphylococcic septicemia, and one from a woman who died 6 days postpartum from decompensation of the heart. Septicemia, especially puerperal sepsis, and verrucose endocarditis appear to be the chief etiologic factors in the causation of infarcts of the hypophysis. Areas of necrosis in the anterior lobe in cases of eclampsia have been described by Merkel and Schmorl; whether these were due to embolic processes was not stated.

Upon gross examination of the hypophysis, infarcts may not be visible, or are easily overlooked. In microscopic sections, infarcts appear as sharply defined areas, more or less wedge-shaped, in which the nuclei do not stain and the cytoplasm of the cells takes the eosin stain. The cell outlines are still visible as in coagulation necrosis elsewhere. At the periphery of the necrotic area there is frequently a zone of leukocytic infiltration, especially in those cases in which the embolus contained cocci. No mention is made of a zone of hyperemia surrounding an infarct of the hypophysis, such as is seen about an infarct of the kidney.

If the patient survives the pathological condition which is responsible for the infarct of the hypophysis, the area of necrosis undergoes simultaneous resorption and organization by the ingrowth of connective tissue, in the same manner as in infarcts of any other organ. The final result is a wedge-shaped scar at the site of the infarct. Such scars in the hypophysis are usually accompanied by scars ("ancient infarcts") in the kidneys and spleen.

If the infarct is relatively large, there may be destruction of such an amount of the hypophysis as to induce disturbances due to diminished function of the anterior lobe. The cases of Merkel, or Fraenkel(*b*), and four of Simmonds'(*g*) cases were women who, after the birth of their last child, from 9 to 11 years before death, suffered from puerperal sepsis. This was followed by cessation of menstruation and by progressive weakness and emaciation. Simmonds'(*g*)(*n*) fifth patient was a dwarf, with hypoplasia of the genitals and lack of secondary sex characteristics. In all seven of these cases, autopsy revealed an almost complete replacement of the anterior lobe of the hypophysis by dense fibrous tissue, without other lesions in the other organs of the body to account for the clinical manifestations, except a carcinoma of the stomach in one of Simmonds' patients.

The lesion of the hypophysis in each instance was believed to be the result of an old embolic process occurring in the women as an accompaniment of puerperal sepsis, and in the dwarf, during the very early days of life.

From these cases it appears probable that a fairly well defined train of results follows infarction of a considerable part of the anterior lobe of the hypophysis. In adults there develops a progressive cachexia; loss of teeth, and of scalp, axillary and pubic hair; and atrophy of the genital organs. If the embolism and infarction occur in the early days of life, dwarfism and hypoplasia of the genitalia and failure to develop the secondary sex characteristics result.

Necrosis and Calcification

Necrosis may occur in the hypophysis as a result of infarction; or of trauma; or of infections of the gland itself, especially the infection granulomas; or of the effects of toxic substances. It may take the form of coagulation necrosis, as in infarction and in infection granulomas; or liquefaction necrosis, as in acute suppurative inflammation. Coagulation necrosis is usually anemic in type; more rarely it is accompanied by hemorrhage into the necrotic area as in the cases of Berblinger(*c*) and of Merkel. Gierke(*b*) states that arteriosclerosis and syphilitic arteritis can cause ischemic necrosis of the hypophysis. Schilder found a small area of necrosis in the anterior lobe in which the lumen of the vessels was much narrowed by deposits of amyloid.

Necrosis of toxic origin is less well understood. Boehncke and Koch, and Creutzfeld and Koch observed in the pars intermedia of the hypophysis of children dead from diphtheria, nuclear changes characteristic of necrosis, namely, margination of the chromatin, pyknosis, karyorrhexis and karyolysis. Similar changes were found in the hypophyses of guinea pigs which had succumbed to subcutaneous injections of diphtheria bacilli. Schmorl has observed similar necrotic processes in diphtheria.

Necrosis of the hypophysis occurs occasionally in eclampsia. Schmorl found small areas of necrosis in two cases of this disease. Berblinger(*c*) has described an almost total necrosis of the hypophysis in a case of eclampsia. These changes in the pituitary body appear to resemble those found in the liver in this disease. Whether they are due to the direct action of some toxin, or to a thrombosis of the capillaries, as shown by Ewing in the case of the liver, cannot now be stated. Necrosis of the hypophysis in eclampsia is probably not common, for, as pointed out by Schmorl, the lesion is not mentioned by Erdheim and Stumme in their study of a large series of cases.

Coagulation necrosis also occurs commonly in the central portions of tumors of the hypophysis.

Calcification may take place in the hypophysis, as in other organs, in areas of necrosis. It is found more commonly in necrotic processes in tumors than in areas of dead tissue resulting from other lesions. Extensive calcification in tumors has been observed by Erdheim(*b*), Konjetzny, and others. Kraus has described "calcareous degeneration" of the hypophysis, and Bayon, in a cretin, observed a "sablous" transformation of the hypophysis similar to that commonly found in the pineal gland. Halliburton and Candler encountered a hypophysis in an insane person, that was cystic and so infiltrated with lime salts that they were unable to obtain sections for microscopic study. There was apparently nothing in the clinical manifestations to indicate a lesion of the hypophysis.

Degenerations

Fatty Changes.—The amount of fat and lipoids in the cells of the anterior lobe of the hypophysis increase with age as pointed out by Erdheim(*a*) and Kraus(*a*). Virchow mentions fatty degeneration of the glandular portion. Merkel found fatty degeneration in the peripheral parts of an anemic infarct of the hypophysis. Thom mentions fatty degeneration of the anterior lobe in a case of carcinoma, the site of which was not stated. Schmidtmann describes fatty changes in the hypophyseal cells in tuberculosis. Kraus(*a*) believes that the cell lipoids of the hypophysis are not secretion products, but are an expression of depressed cell function; and that the appearance of doubly refractile intracellular substances is an indication of cell death.

Hyaline degeneration is not uncommon in the walls of the vessels of the hypophysis and in the connective tissue (Schmidtmann, Schmorl, and others). This is especially true of those cases showing fibrosis, either generalized or localized, as in ancient infarcts.

Amyloid degeneration has been observed occasionally, and would probably be found more frequently if the hypophysis were systematically examined in those cases in which amyloid is present in other organs. Simmonds(*f*) states that it is common in cases of general amyloidosis. Schmidt(*d*) reports 4 cases of widespread amyloid degeneration, in one of which he found it also in the hypophysis. Davidsohn, Schmidtmann, and Pepere also mention its occurrence. Schilder has described its distribution in the hypophysis of a 45-year-old man who died of chronic tuberculosis of the lungs. There were widespread deposits of amyloid in many organs of the body. In the hypophysis it was present in the walls of the small blood vessels and capillaries to such an extent that in places it exceeded in amount that of the cells themselves and greatly narrowed the

lumina of the vessels. The anterior lobe was more markedly affected than the posterior, where it was found only in the walls of the larger vessels.

Myxomatous changes in the posterior lobe were observed by Boyce and Beadles(*b*) in "a few cases."

Colloid is normally present in amounts increasing with age, in the pars intermedia, and in much smaller quantities in the alveoli of the anterior lobe. The colloid is sometimes greatly increased, usually occurring in large and small cysts in the pars intermedia. In the anterior lobe it is also occasionally found in excessive amounts in small cyst-like cavities, the result of overfilling of the gland acini; and also as masses of homogeneous material in the thin-walled blood vessels. Thom observed "hypercolloidosis" of the hypophysis in a case of "carcinoma of the liver" with marked icterus. He thought that the bile was a factor in the production of the colloid, because Hüthle found it increased in the thyroids of dogs suffering from jaundice due to ligation of the common bile duct. Strauch has recorded excessive amounts of colloid in the acini of the hypophysis of a 9-year-old girl with hydrocephalus associated with polydipsia, polyuria and adiposity. Boyce and Beadles(*a*) observed an increase in extra-acinar colloid in cases of myxedema. Schoenemann studied 112 hypophyses and classified them in 5 groups. In the 5th group of 9 cases he placed those showing marked colloid production.

Glycogen is present in all of the organs of the body as an integral part of the cells. In a few organs, especially the liver, it is also present as a result of storage. Neubert has studied the glycogen content of the hypophysis and found it increased in diabetes mellitus.

Pigmentation

In the neurohypophysis there is usually present yellow to yellowish-brown pigment. Ordinarily it is not abundant; occasionally it may be sufficient in quantity to give the posterior lobe a brownish color. As a rule it is not diffusely distributed through this part of the gland, but is collected in one or more rather circumscribed areas. Much of it is apparently intracellular; but it also appears in small irregular clumps that cannot be associated with any cell. It is neither lipochrome nor melanin. It is not crystalline, like hematoidin, and does not give the microchemical test for iron like hemosiderin. In one of my specimens it surrounded a space which was present in a large number of serial sections, thus somewhat resembling an "apoplectic cyst" of the brain. It did not give the reaction for iron, and was not, therefore, of hematogenous origin.

The chemical nature of this pigment is not understood. According to Clunet and Jonnesco, and Kanavel and Lewis it is not changed by the

various fixing fluids. It is not dissolved by benzine, chloroform, ether, xylol, or boiling alcohol. It is not stained by ordinary hematoxylin, eosin, triacid stain, Sudan III nor Scharlach R. It stains dark with iron-hematoxylin. If fresh specimens are allowed to stand for 24 hours in osmic acid, the pigment assumes a dark brown color, or becomes greenish-black.

Its origin is not definitely known. According to Kohn(*a*) the glia fibrils of the neurohypophysis are the chief seat of the accumulations of the pigment. He is not certain, however, that it is derived from these fibrils. Tello, on the other hand, thinks that the pigment is derived from the disintegrated neural elements themselves. Stumpf(*a*)(*b*) and Vogel believe that it comes from cells of the anterior lobes, especially from basophilic cells, that have wandered into the neurohypophysis. They assert that the amount of pigment present is closely proportional to the destruction and disintegration of those cells that find their way into the posterior lobe. Tölken, on the other hand, disputes the alleged "wandering" of cells from the anterior into the posterior lobe. Epithelial cells resembling those of the anterior and middle lobes are unquestionably found in the neurohypophysis. But Tölken, by the study of serial sections, was able to show they were the result of growth backward of "embryonal cells" of the intermediate zone; and that what appeared, in single sections, to be isolated cells or groups of cells, were merely parts of cell cords which had grown into the posterior lobe from the pars intermedia. He found this process of backward growth in 50 out of 105 hypophyses examined by him. He does not, therefore, accept Stumpf's theory of the origin of the pigment.

The significance of the pigment in the neurohypophysis is as little understood as is its origin. Fischer(*c*) does not believe that it has any pathologic significance. Dammann found it increased in amount in the hypophysis from a patient with adiposis dolorosa. According to Stumpf (*a*) it is absent in the newborn, in pregnant women and in those recently delivered. Vogel found no increase in the pigment in tabes, "paralysis" and cachexia. Schmidtmann observed an increase in tuberculosis. Lewis examined "several" hypophyses for pigment and found the amount so variable that he was unable to form any opinion as to the physiologic activity of the posterior lobe from the amount of pigment present. In my own series I have met with the same remarkable variations in the amount of pigment present and have been unable to associate its presence in exceptional quantities with any other pathologic processes or with any special clinical symptoms.

Iron-containing pigment does occasionally occur in the hypophysis, as might be expected, since the gland is sometimes the seat of hemorrhage. Luzzatto and Lubarsch have described the presence of pigment of hematogenous origin.

Changes in the Hypophysis in Infectious Diseases

The anterior lobe of the hypophysis is a functionating gland. It would not be surprising, therefore, to find that it is affected by the same types of parenchymatous degeneration in acute infectious diseases associated with high temperatures, as are found in other glands of the body, such as the liver and kidneys. However, I have not found in the literature any reference to cloudy swelling of the hypophysis. This may be due to the difficulties encountered in making any kind of gross anatomic diagnosis of lesions of the hypophysis.

Creutzfeldt and Koch, and Boehncke and Koch found the pars intermedia greatly changed in 7 out of 9 patients dead of diphtheria. These included deaths from general intoxication with diphtheria toxin and from sudden cardiac paralysis. The changes consisted in margination of the chromatin, pyknosis, karyorrhexis, and karyolysis, i. e., necrosis, of the cells of the middle lobe. They produced similar changes in the hypophyses of guinea pigs by the injection of pure cultures of diphtheria bacilli. The injury to the pars intermedia was greatest in chronic poisoning of the animals. These authors advanced the conception that these lesions of the middle lobe are an important factor in those cases of diphtheria in which the circulation fails before there is clinical evidence of changes in the heart itself. At autopsy they found the lesions in the heart insufficient to account for the severe atony of the vascular system. This conception may well be questioned without more definite evidence. Schmorl observed areas of necrosis in the hypophysis in diphtheria, without specifying their location. Abramow has also studied the changes in the hypophysis produced in guinea pigs in experimental infection of these animals with diphtheria. He does not mention necrosis of the cells of the pars intermedia; but found quite constantly hyperemia, diminution of eosinophil cells, and the appearance of cells with non-staining cytoplasm. In the second week of the intoxication, these latter cells had greatly increased in numbers and the eosinophils had almost entirely disappeared. Abramow considered these elements to be eosinophilic cells that have become exhausted as a result of excessive activity.

Pirone(*a*)(*c*) has studied the histologic alterations in the hypophyses of 8 human subjects, 7 dogs, and 30 rabbits, dead of hydrophobia. He found in the posterior lobe lymphocytic infiltrations, usually perivascular, but sometimes diffuse, and occasionally nodular, in distribution. These resembled somewhat the changes commonly found in the Gasserian ganglion in hydrophobia. There was also present hyperemia of the anterior lobe with slight "degenerative changes" in the epithelial cells. These alterations were more pronounced in the protracted cases than in those that were more rapidly fatal. Pirone(*b*) also found that the hy-

pophyses of dogs with "street rabies" contained the virus of the disease. He believed that the continuity of the neurohypophysis, through the infundibulum, with the ventricles of the brain to be an important etiologic factor in the pathogenesis of the changes which he observed.

Dialti observed changes which he thought due to increased activity of the cells of the anterior lobe, in typhoid fever, pneumonia, and uremia. In tetanus, smallpox, septicemia, hydrophobia and meningitis he encountered changes of a degenerative character in the hypophysis. In tuberculosis, Thom found the hypophysis frequently enlarged and sometimes hyperemic. Dialti and others have recorded proliferation of connective tissue in the anterior lobe in chronic tuberculosis of the lungs. This is not characteristic of this disease, however, for it is not infrequently observed in connection with other pathological conditions. Thaon(*a*) studied the hypophyses from 23 tuberculous individuals. In one instance he found a small area of necrosis which was not a tubercle. In a number of the cases there was proliferation of connective tissue, and, more rarely, perivascular accumulations of leucocytes. Schmidtmann, in a considerable number of cases of tuberculosis, observed the following changes in the hypophysis: Hyaline degeneration of the walls of the blood vessels, fatty changes in the cells of the anterior lobe, amyloid degeneration, and increased pigment in the neurohypophysis.

Alterations in the Hypophysis Associated with Changes in the Thyroid Gland

The presence of colloid in the hypophysis and certain resemblances in the histologic structure of the pars intermedia to that of the thyroid, early led to attempts to correlate the functions of these two glands. The problem has been studied from material obtained at autopsy and by experimental methods.

Schoenemann examined the hypophyses and thyroids from 112 bodies and attempted to correlate the changes found in them without arriving at any definite conclusions. Tölken examined the hypophyses from a large number of individuals with simple colloid goiter and found no noteworthy changes in size, weight or histologic structure. It would appear, therefore, that simple goiter is not accompanied with alterations in the hypophysis.

Very little attention appears to have been paid to the condition of the hypophysis in exophthalmic goiter. Benda(*a*) examined 3 cases. In 2 of these the hypophysis was small and firmer than normal; the connective tissue was increased, and the alveoli were small and contained few chromophil cells. The cells were atrophic, vacuolated and contained dark pigment. In the third case the hypophysis showed no gross changes. Micro-

scopically, areas of normal histologic structure alternated with places showing the changes observed in the other two cases. Lewis(*a*) studied the hypophysis of a woman aged 50 years, who suffered from exophthalmic goiter. The stroma of the anterior lobe was increased, the alveoli reduced in size and, although the chromophil elements were normal in number, they were smaller and more vacuolated than in the normal gland. No brown pigment was present. Lewis concluded that this hypophysis did not function normally. Hofstätter (*a*) also found changes in the hypophysis in this disease, which he thought might be concerned in some of the associated symptoms, for example, the temperature changes, polyuria, polydipsia.

In congenital myxedema and cretinism enlargement of the hypophysis has been described by Comte, Boyce and Beadles(*a*), Ponfick(*a*)(*c*), Josefson, Bernardini, and others. In Boyce and Beadles' case the hypophysis weighed 1.21 grams and the anterior lobe "showed every appearance of functional activity." Josefson's patient exhibited an adenoma of the hypophysis. One of Ponfick's cases showed a small fibrous hypophysis, and in a third the hypophysis was entirely absent. Schoenemann records the case of a cretin whose hypophysis was "quite small," the chromophil cells were few in number, and the colloid scanty in amount. De Coulon examined the hypophyses of seven patients showing varying degrees of cretinism. In one, the hypophysis was smaller than normal, in another it was about normal in weight, while in the remainder the weight was from one and one-half to three times the normal. The cords of cells were small and did not fill the spaces which they occupied; colloid was scant; there was usually an increase of connective tissue and a very noticeable dilatation and overfilling of the blood-vessels. In four of his cases the chromophil cells were numerous. The cases of Zuckermann and Bayon showed increase in the number of chromophil cells.

Boyce and Beadles(*a*), Comte, Bayon, and Zuckermann believed that the changes in the hypophysis in cretinism were of the nature of a compensatory reaction, and an attempt on the part of this gland to act vicariously for the thyroid. From a careful study of the cases reported in the literature it is evident that in some cases of myxedema and cretinism the hypophysis is atrophic (Ponfick(*a*), de Coulon). Whether atrophy of the hypophysis is associated with more severe degrees of myxedema and cretinism could not be positively determined from the records at hand. The data available are therefore too meager to justify a definite conclusion in regard to the effect of changes in the hypophysis upon these diseases.

The condition of the hypophysis in cachexia thyreopriva has not been extensively studied in man. Schoenemann mentions the case of a 25-year-old man who, 6 years before death, had undergone a thyroidectomy and thereafter suffered from cachexia thyreopriva. His hypophysis weighed 1.59 grams; the chromophil cells were very numerous and the colloid fairly abundant.

The effect of thyroidectomy upon the hypophysis has been made the subject of numerous studies in animals. The majority of investigators, such as Rogowitsch, Stieda, Leonhardt and Cimorini, report enlargement of the anterior lobe following removal of the thyroid in animals. They believe that this enlargement is of the nature of a compensatory hypertrophy and an attempt on the part of the hypophysis to functionate vicariously for the thyroid. Trautmann, on the other hand, after an elaborate study of the problem in goats, could not positively determine an increase in size of the hypophysis of the thyroidectomized animals; and he believed that the alterations which he found in the anterior lobe were of a definitely regressive nature.

Inflammation

Pyogenic Infections.—Inflammation of the hypophysis may be either acute or chronic. Acute inflammation is usually purulent in character and occurs in two forms: (a) as a relatively large abscess or a diffuse purulent infiltration which may destroy the entire gland or only the anterior lobe; and (b) as minute abscesses, the result of the lodgment of mycotic emboli. The latter are found more frequently in the posterior lobe.

Large destructive abscesses usually occur in connection with some suppurative inflammatory process in the immediate vicinity of the sella turcica. Harvey, Meyer, and Boggs and Winternitz have reported such infections of the hypophysis associated with purulent inflammation of the sphenoidal sinuses; Glinski, Smoler, and Thom found suppurative hypophysitis accompanying purulent leptomeningitis. More rarely the formations of large destructive abscesses in the hypophysis is a part of a general pyemia, as, for example, in one of Glinski's cases. Abscesses of the hypophysis have also been reported by Heslop and by Battiscombe. The entire hypophysis may be destroyed and the sella turcica be occupied by a sac filled with pus, as in the cases of Smoler and of Meyer. In other instances the hypophysis may be changed into a soft, dark red, friable mass, densely infiltrated with pus cells without extensive liquefaction necrosis and definite abscess formation, as in the case of Boggs and Winternitz.

Abscess of the hypophysis being an acute process and usually associated with some other serious disease, death ordinarily occurs before there is time for the development of symptoms of hypopituitarism. The patients of Meyer and of Smoler, however, showed marked adiposity; in the latter there appears to have been a cyst which was operated upon, death following the operation. Harvey's patient suffered a sudden and complete amaurosis.

The relative infrequency with which suppuration of the hypophysis accompanies purulent inflammation in adjacent structures is very striking.

It is possible that this rarity is connected with the alleged absence of lymphatics in the hypophysis (Thaon(*b*)). Without lymph vessels, infection cannot readily spread by contiguity through the capsule of the hypophysis from an infected sinus or from a leptomeningitis.

Small abscesses due to the lodgment of mycotic emboli appear more commonly in the neurohypophysis. Simmonds(*g*) has reported 4 such cases; and Schmorl mentions having observed the condition. The lesion consists of a localized collection of polymorphonuclear leukocytes, with liquefaction necrosis of the central portion of the mass. The chief etiologic factor is septicemia, especially puerperal sepsis.

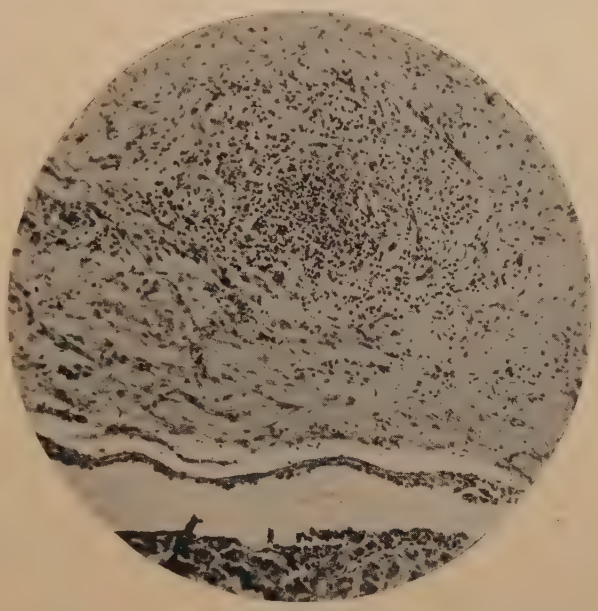


Fig. 2. Small abscess in the anterior part of the neurohypophysis. Magnified 120 times. From a patient with malignant endocarditis with multiple septic infarcts in the kidneys, spleen and brain.

The healing of an abscess of the hypophysis is similar in process to the repair of a similar lesion in any other organ, namely, the resorption of the exudate and replacement of the destroyed parenchyma by scar tissue. It is possible, therefore, for suppurative inflammation of the hypophysis to destroy a sufficient quantity of the gland to cause hypopituitarism in those patients who survive the acute process. Thus v. Hann reports three cases of diabetes insipidus in which he found a sclerosing inflammatory process in the posterior lobe of the hypophysis. Ronchetti found the hypophysis almost entirely destroyed and in its place an inflammatory new formation.

A diffuse fibrosis of the anterior lobe, frequently considered a type of chronic inflammation, is quite common in the hypophysis in old age (Thom and Schoenemann); or associated with chronic tuberculosis of the lungs (Thaon(*a*), Dialti, and others); or in primary atrophy of the hypophysis (Cagnetto(*b*)); in heavy drinkers and in severe arteriosclerosis (Simmonds(*b*)); in scleroderma (Alquier and Touchard); and in cases without definite associated pathological processes (Schmorl, Fraenkel(*a*), and Munson and Shaw). In three of Fraenkel's cases the induration was so marked as to suggest the "cirrhosis of the pancreas sometimes observed in

diabetes mellitus." More rarely, the anterior lobe or even the whole hypophysis may be replaced by mature connective tissue as in the cases recorded by Ronchetti, Fahr, Boyce and Beadles(*b*). V. Gierke(*a*) has reported the case of a man, aged 23, who passed from 4 to 5 liters of urine per day, and whose hypophysis, at autopsy, showed a normal anterior lobe with the neurohypophysis densely infiltrated with lymphocytes and a smaller number of eosin-staining cells. No tubercle bacilli were found and there was no evidence of syphilis in the body. V. Gierke therefore considered the lesions as "some kind of chronic inflammation."

Syphilis of the Hypophysis.—In acquired syphilis lesions of the hypophysis are rare and usually occur in the form of gummas. In the congenital form, there is usually a diffuse indurative process, and, more rarely, gummatous areas. In 1,500 hypophyses studied by Simmonds(*f*) syphilitic changes were observed 9 times. Schmorl mentions two gummas of the hypophysis in acquired syphilis, a scar probably the result of a healed gumma, and frequently diffuse proliferation of connective tissue in syphilitic individuals, without giving further details. Benda(*c*) also mentions 3 gummas of the hypophysis observed by him. I have collected from the literature records of 26 gummas of the hypophysis (Wagner, Weigert(*a*), Barbacci, Birch-Hirschfeld, Hektoen, Troisier, Beadles, Sokoloff, Hunter(*a*), Kufs(*a*), Stroebe, Poscharisky, Starck, Chiari, Bianchi, Goldzieher, Simmonds(*i*), Fry, Woolley, Berge and Schulmann, and Versé, each one case; Schmorl, 2 cases; Benda(*c*), 3 cases; and Simmonds(*g*), 9 cases, without details). Two of the above 26 cases were in congenital syphilis, the remainder in the acquired form. The above list includes a case reported by Wagner as tuberculosis of the hypophysis, but which has been classed by Heidekamp and others as a gumma.

Uncertainty attaches to all of the cases of both tuberculosis and gummas of the hypophysis reported before the discovery of the tubercle bacillus.

Gummas of the hypophysis are found in the anterior lobe more commonly than in the posterior. They are usually single but may be multiple, as, for example, the case of Berge and Schulmann, in which 8 gummas were found, most of them in the posterior lobe. Occasionally the entire gland is affected as in the case of Hektoen. A hypophysis that is the seat of a gummatous process is usually larger than normal, although the actual weight has been recorded in very few cases. In the case reported by Hektoen the gland weighed 1.8 grams. In other instances the size of the hypophysis is described as that of a "cherry seed," or a "small nut," or "a walnut," or "a small marble," or "a pigeon's egg."

A gummatous hypophysis is usually adherent to the sella turcica, and its capsule is thickened. The consistency is usually firmer than normal. On surfaces made by sectioning the color is yellowish-white, or grayish-yellow, or grayish. In some instances the central portions are definitely

caseous. Microscopically, there is caseation, with surrounding capsule of connective tissue and round cell infiltration. Giant cells are only very rarely present. In other instances the anterior lobe, or even the entire hypophysis, is diffusely infiltrated with round cells, with scattered irregular patches of necrosis.

Satisfactory details as to the clinical manifestations and associated pathology are not given in many of the reported cases of gumma of the hypophysis. Gummas or scars believed to be due to healed gummas in other organs are recorded in the reports of the 26 cases as follows: meninges, 4 times; skull, including the nose, 5 times; liver, 6 times; various bones other than the skull, twice; kidneys, twice; adrenals and vagina, once each. Polyuria is reported as a symptom twice (Goldzieher, and Berge and Schulmann); in each case the gumma was in the posterior lobe. "Marasmus" of two months' duration was present in Sokoloff's patient. Partial blindness is mentioned once (Chiari).

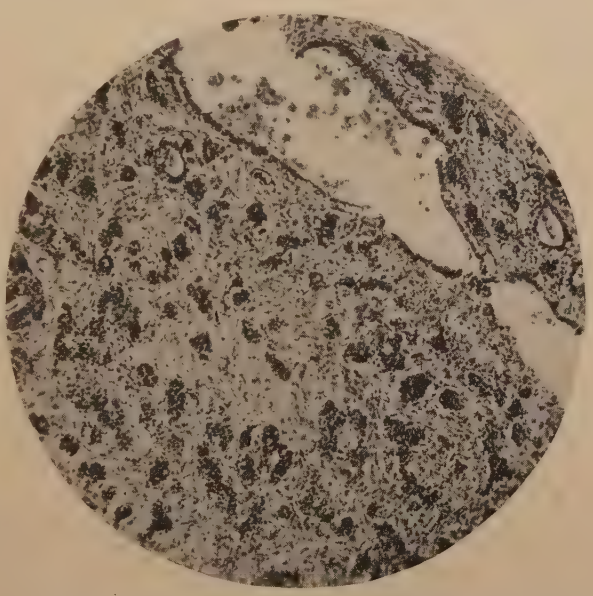


Fig. 3. Congenital syphilis of the hypophysis. Marked proliferation of connective tissue in the anterior lobe. Magnified 110 times.

Syphilitic changes in the hypophysis usually occur late in the course of the disease. Simmonds'(*i*) patient, however, was a man 78 years old, who acquired syphilis only 4 months before death. In addition to the gumma of the hypophysis, there were multiple gummas in the lungs in which spirochetes were demonstrated.

Luetic infections of the hypophysis are more frequent in congenital than in acquired syphilis. In 16 congenitally syphilitic newborn, Simmonds(*b*) found luetic changes in the hypophysis 6 times. In the congenital form of the disease the alterations in the hypophysis are usually a diffuse proliferation of connective tissue (Simonds, Simmonds(*b*), Schmorl). (See Fig. 3.) More rarely they appear as localized growths of connective tissue with necrosis at the center, miliary gummas (Simmonds(*g*), and Schmorl); or there may be larger gummas (Chiari, and Versé). In one newborn syphilitic infant Schmidt found necrosis of a large part of the

anterior lobe without the formation of gummas, and with only slight proliferative changes in the connective tissue.

Few or no clinical data are given in the records of cases of congenital syphilis of the hypophysis. With few exceptions the lesions have been studied in the hypophyses of infants that were still-born or who died a few hours or days after birth. Chiari's patient was 9 years old, and showed a gumma of the anterior lobe. In my case spirochetes were present in great numbers in the anterior lobe, fewer in the neurohypophysis.

Tuberculosis of the Hypophysis.—Tuberculous infection of the hypophysis is not uncommonly associated with chronic tuberculosis of the lungs, and is quite common in general miliary tuberculosis. The lesion appears either as a conglomerate tubercle or as one or more miliary tubercles. I have found records of 28 cases of tuberculosis of the hypophysis. Of these 10 were miliary in type (Lancereaux(*a*), Lucien and Parsitot, Simmonds(*d*) (4 cases), and Schmidtmann (4 cases); and 18 were conglomerate tubercles (Beck, Boyce and Beadles(*b*), Hütor, Haushalter and Lucien, Cushing(*a*), Sommer, Heidekamp, Glinski, Zenoni, Bland-Sutton, v. Hann, Froboese, Schmidt(*c*), Valenta, each one case; and Schmidtmann and Schmorl, each 2 cases). In 3 additional instances (Simmonds (*d*), and v. Hann) a scar was found in the neurohypophysis of tuberculous individuals, and the authors considered them to be the result of a healed tuberculous process. In two other cases Schmidtmann observed miliary tubercles in the capsule of the anterior lobe in patients with tuberculous meningitis.

Conglomerate tubercles commonly affect the anterior lobe, sometimes the entire gland. The hypophysis which is the seat of such a lesion is usually enlarged, is adherent to the sella, the capsule is thickened, and the whole gland is firmer than normal. The amount of accompanying fibrosis varies. Occasionally a part of the anterior lobe is composed of connective tissue so dense as to be of cartilaginous consistency, as in the case of Boyce and Beadles(*b*). On surfaces made by sectioning the central part of the tuberculous portion is caseous; the peripheral part, fibrous. Microscopically the appearance is that of a conglomerate tubercle in other parts of the body. Giant cells are usually fairly numerous.

Miliary tubercles are more frequently found in the posterior lobe. They are often not visible even on very careful macroscopic examination. Microscopically they do not differ from similar lesions in other organs.

Etiologically, tuberculosis of the hypophysis may be classified as (a) metastatic, and (b) as extension to the hypophysis from adjacent structures. The latter form is rare and usually results from involvement of the hypophysis from a carious process in one of the bones of the base of the skull, especially of the body of the sphenoid bone, as in the cases of Sommer and Heidekamp. The metastatic form is usually, but not always, miliary in type. Miliary tubercles of the hypophysis are frequently associated

with tuberculous meningitis, in my collected series of 10 cases, the presence of tuberculous meningitis is mentioned specifically in 7 instances. In all of these cases there was also acute generalized miliary tuberculosis. The main body of the hypophysis is rarely involved in those cases of tuberculous meningitis not associated with generalized miliary tuberculosis. Simmonds(*j*), however, found the infundibulum almost always infected in tuberculous meningitis, the process being limited to a more or less thick infiltration about the infundibulum and, somewhat less frequently, an infiltration of the capsule of the gland. In 7 cases of tuberculous meningitis not associated with general miliary infection, Hüter found the hypophysis free, although in two of the cases there were miliary tubercles in the capsule of the anterior lobe. The infrequency with which the body of the hypophysis is involved in tuberculous meningitis is probably due to the protective action of the capsule and of the covering dura mater; to the very scant vascular connection between the meninges and the hypophysis, this being limited to a very few minute vessels from the leptomeninges to the infundibulum; and, possibly, to the absence of lymphatics in the hypophysis, as asserted by Thaon (*b*).

Tuberculosis of the hypophysis is practically never primary. In the cases of Beck, Zenoni, and Cushing (*a*), only, was it specifically stated that no tuberculosis was found elsewhere in the body.

The two sexes were about equally affected in my collected series of 28 cases of tuberculosis of the hypophysis, notwithstanding Froboese's rather startling statement that tuberculosis of the pituitary body "is seen only in women."

Tuberculosis of the hypophysis is only rarely associated with symptoms referable to that gland, although in many of the recorded cases clinical data are very imperfectly reported. The patients of Boyce and Beadles(*b*) and of Beck were blind; in each instance the anterior lobe was affected and much enlarged. Polyuria or diabetes insipidus is recorded in 4 cases. Hüter's patient was a dwarf. Simmonds (*l*) believes that tuberculosis of the hypophysis may be the cause of "hypophyseal cachexia."

Simmonds(*k*) has recorded the case of an old woman in whose hypophysis he found "true giant cells" adjacent to accumulations of round cells and epithelioid cells. These nodules resembled tubercles, but, Simmonds asserts, they have nothing to do with either tuberculosis or syphilis, and are a "formation *sui generis*."

Actinomycosis of the Hypophysis.—Belkowski has reported a case of actinomycosis of the base of the skull and meninges which began in the sella turcica.

Miscellaneous Lesions of the Hypophysis

Localized accumulations of lymphocytes are occasionally seen in the hypophysis. They are mentioned by Simmonds(*e*). Pirone(*c*) observed round cell infiltration in the neurohypophysis in hydrophobia. Berblinger (*a*) found large accumulations of lymphocytes about a sarcoma which had invaded the posterior lobe through the infundibulum from the brain. Such cells are also abundant about tuberculous and syphilitic lesions of the hypophysis. In two hypophyses which I have studied there were groups of lymphocytes immediately behind the pars intermedia. (See Fig. 4.) One of these hypophyses was from a man who died of chronic diffuse nephritis; the other from a colored male who succumbed to hemorrhagic (lethargic) encephalitis. In the latter case there was also a slight degree of perivascular round cell infiltration in the neurohypophysis similar to that seen in the brain. These localized accumulations of lymphocytes in the hypophysis suggest the similar aggregations so commonly found in the thyroid gland is exophthalmic goiter. Their significance in the hypophysis is not clear, except possibly in the case of encephalitis.

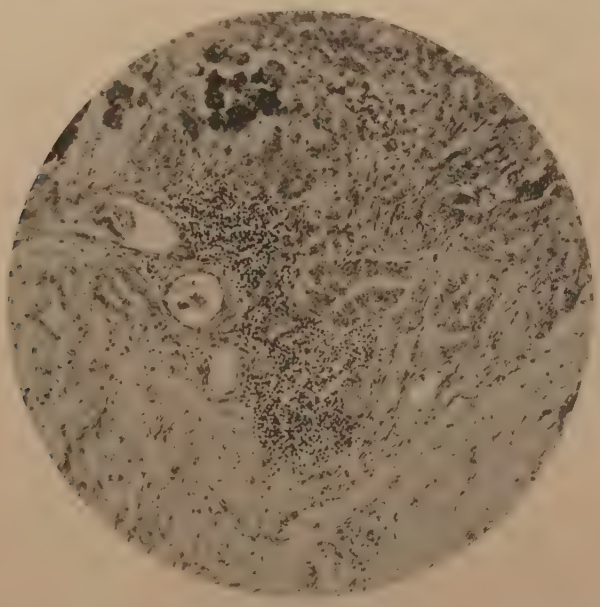


Fig. 4. Area of lymphocytic infiltration in the middle lobe of the hypophysis. Magnified 130 times.

Schmorl noted leukemic infiltration of the hypophysis similar to that seen in the liver and kidneys in leukemia.

Simmonds(*e*) mentions finding abnormal islands of epithelium in the

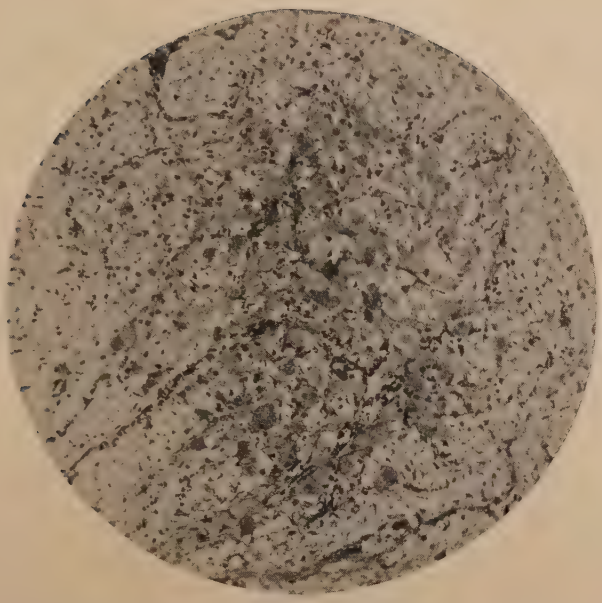


Fig. 5. Group of abnormal, or misplaced, cells in the posterior part of the neurohypophysis. Magnified 130 times.

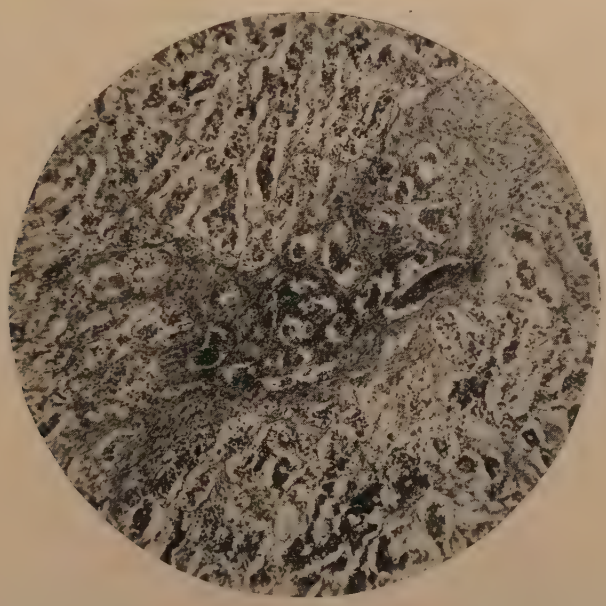


Fig. 6. Hemangioma-like structure in the midst of a lateral half of the anterior lobe of the hypophysis. Magnified 90 times.

hypophysis without giving details as to their location or character. In each of two hypophyses in my collection there was present in the posterior half of the neurohypophysis an isolated "island" of large cells, with abundant cytoplasm filled with small vacuoles and with deeply staining oval nuclei located in the periphery of the cells. (Fig. 5.) In serial sections these masses were found not to be connected with the anterior lobe. These cells do not resemble any of those commonly found in the anterior lobe.

There is normally present at about the center of each lateral half of the anterior lobe a mass of connective tissue from which smaller bands radiate to form the delicate stroma of the gland. In these masses of fibrous tissue there are normally several blood vessels. In a considerable percentage of hypophyses these vessels are increased in number and size so that the whole central mass is composed of wide blood spaces separated by narrow bands of connective tissue, thus resembling a so-called hemangioma cavernosum of the liver. (See Fig. 6.) Evans and Assinder have described an angioma of the hypophysis.

Aplasia, Hypoplasia and Atrophy

Absence of the hypophysis has been discussed in the paragraphs on Malformations.

In dwarfs the hypophysis has been found hypoplastic by Hutchinson and Sternberg(*b*). The underdevelopment affected the anterior lobe chiefly. In Hutchinson's case this lobe formed barely one-third of the total mass of the gland, instead of the normal five-sixths.

Atrophy of the hypophysis may be either primary or secondary. Primary atrophy occurs quite constantly in old age and is an expression of physiologic regression on the part of the gland. The upper surface sinks in, thus deepening the pit which is normally present there and causing an apparent lengthening of the infundibulum. There is almost constantly an accompanying increase of connective tissue, and frequently a simultaneous widening of the blood vessels. This senile atrophy of the hypophysis is often accompanied by, and probably partly due to chronic endarteritis (Cagnetto(*b*)). The epithelial cells of an atrophic gland diminish in size; their cytoplasm becomes less granular, and the nuclei are usually smaller and stain more deeply. In such an hypophysis there may be localized areas in which the cells appear to be hyperactive, and are crowded with granules and vacuoles. Primary atrophy does not appear to induce symptoms of hypopituitarism.

Diminution in size, a sort of temporary atrophy, of the anterior lobe has been described by Cushing and Goetsch(*b*) and by Mann in hibernating animals.

Secondary atrophy results from pressure by tumors, by aneurysms (Mitchell, Kümmell, and Rheinhardt), or by internal hydrocephalus.

Tumors of the Hypophysis

General Discussion.—Hyperplasias and true neoplasms of the hypophysis are the lesions of this gland which have been most thoroughly studied and most copiously reported. This is true because these are the most obvious changes noted upon gross examination at necropsies; because they give rise to symptoms which are most easily recognized clinically; and because they are frequently amenable to successful surgical treatment.

Certain difficulties, which at present appear to be insurmountable, attach to the study and diagnosis of tumors of the hypophysis, and to educing trustworthy generalizations from the collection and analysis of records of cases reported in the literature. In the first place, the normal histology of the hypophysis is still a matter of some uncertainty. Three types of cells are now generally recognized in the anterior lobe: (a) the chromophobe, non-granular, or chief cells; (b) eosinophile cells, which contain granules that take acid dyes like eosin; and (c) basophile cells, which contain granules which stain with basic dyes like hematoxylin. The relation of these cells to each other has not been firmly established. Benda (*a*) believed that these three so-called types represented different stages in the secretory activity of one and the same kind of cell. Scaffidi, on the other hand, considers eosinophiles and basophiles as separate and distinct types of cells. Kraus(*b*)(*c*) believes that the granular cells originate from the chief cells in a very definite manner and are not transformed one into the other. He differentiates five types in the anterior lobe of the hypophysis, from any one of which characteristic tumors may arise: chief cells; transitional cells, the stage of transformation of chief into one or other of the kinds of chromophile cells; eosinophilic and basophilic cells; and the cells of pregnancy.

The lack of a uniform terminology raises serious obstacles, both in the classification of neoplasms of the hypophysis, and in determining the fundamental pathologic process underlying acromegaly and Fröelich's syndrome. These difficulties are due in part to the uncertainty as to the normal histologic structure of the anterior lobe, especially as regards the histogenesis of its component cells. Furthermore, in tumors affecting the anterior lobe, the cells tend to lose some of their more highly differentiated qualities and do not show the characteristic granules as distinctly, nor in such numbers, as in the normal gland. However, by the use of special stains employed by Benda(*a*), Scaffidi, and Lewis(*a*), these granules can be demonstrated in some of the cells of even very malignant tumors of the anterior lobe of the hypophysis. It is evident that the terms "hyper-

plasia," "struma," "adenoma" and "sarcoma" have frequently been used by different authors for the same pathologic condition.

In order to establish some uniformity in the histologic diagnosis of tumors of the anterior lobe of the hypophysis, the following terminology is suggested as at least tentatively useful:

(1) *Hyperplasia.*—A moderate, uniform enlargement of the hypophysis due to increase in size and number of the cells of the anterior lobe. This term should be limited to those more or less physiological enlargements of the hypophysis which accompany pregnancy, follow castration, or are frequently associated with hypothyroidism. The weight of the gland rarely exceeds 1.5 grams.

(2) *Struma Pituitaria.*—In the sense in which the term was used by Virchow—namely, a uniform enlargement of the anterior lobe due to multiplication of its cells. The size may vary from that seen in hyperplasia to several centimeters in diameter.

(3) *Adenoma.*—A sharply circumscribed growth composed of epithelial cells, within the hypophysis. The hypophysis may or may not be enlarged. That part of the anterior lobe outside the circumscribed nodule has its normal histologic structure.

(4) *Carcinoma.*—A malignant epithelial tumor characterized by multiplication of the cells of the anterior lobe, with invasion of the capsule and adjacent structures.

In each of the above types of hyperplasias and tumors a modifying word or phrase, such as "chief cell," "eosinophil cell" or "basophil cell," should be employed to designate the histogenesis of the process.

(5) *Sarcoma.*—This term should be limited to those malignant tumors of the hypophysis in the cells of which granules cannot be demonstrated by the special stains mentioned above.

To determine the relative frequency of the different types of tumors of the hypophysis is difficult because of the evident differences in the nomenclature used by the various authors. The following table (I) is based upon an analysis of records of 275 neoplasms of the hypophysis collected from the literature together with a small number in my own collection and in the Museum of Pathology of the Northwestern University Medical School. In this table, I have included, under "Strumas," those cases, other than pregnancy, castration and hypothyroidism, that had been diagnosed "hyperplasia" or "hypertrophy" by the authors reporting them. From this table it is seen that the tumors, in the order of their frequency, are adenomas, 91; cranio-pharyngeal duct tumors, 50; strumas, including the so-called hyperplasias, 39; and sarcomas, 38. It is certain that many of the growths of the hypophysis that are classed in the table as adenomas were strumas, and that many of those classed as sarcomas were probably carcinomas. However, it was found impossible to attempt a rediagnosis of so many of these new growths from the data in the records

TABLE I

Type of Tumor	Males									Females									Sex and Age Not Given	Totals
	Up to 10 yrs.	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	Total	Up to 10 yrs.	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	Total		
Struma	1	0	5	6	4	3	1	0	20	0	0	2	3	1	1	1		8	11	39
Adenoma—Simple	1	3	2	1	9	10	2	2	30	0	2	9	6	7	9	3	2	38	16	84
Adenoma—Malignant ..	0	0	0	1	0	0	0	0	1	0	0	0	4	0	2	0	0	6	0	7
Carcinoma ...	0	0	1	2	0	0	1	0	4	0	0	1	1	1	2	1	0	6	4	14
Cranio-pharyngeal Duct Tumors—Benign	1	3	5	6	1	0	1	1	18	4	2	3	3	4	3	1	0	20	6	44
Cranio-pharyngeal Duct Tumors—Malignant .	0	1	1	1	0	0	0	0	3	0	3	0	0	0	0	0	0	3	0	6
Sarcoma	0	2	0	4	2	0	2	0	10	0	2	6	5	4	2	1	0	20	8	38
Endothelioma.	0	1	1	1	2	0	1	0	6	0	0	0	0	0	0	0	0	0	1	7
Perithelioma .	0	0	0	1	0	0	0	0	1	0	1	0	1	0	2	0	0	4	2	7
Teratoma	1	1	1	2	0	0	0	0	5	0	1	0	0	0	0	0	1	2	2	9
Lipoma			1						1									0	0	1
Glioma			1						1				1					1	1	3
Lymphadenoma									0							1		1	0	1
Myxoma																			1	1
Angioma					1				1									0	0	1
Psammoma ...											1							1	1	2
Metastatic Tumors	1	1	0	0	0	1	0	0	3	0	0	0	1	2	1	1	0	5	3	11
Totals									104									115	56	275

that it was finally decided to classify them in the table just as they had been diagnosed by investigators who reported the cases.

From this table it is also apparent that there is no very noteworthy difference in the relative frequency of tumors and hyperplasias of the hypophysis in the two sexes.

In Table II is shown the relative frequency with which acromegaly, Fröelich's syndrome, and diabetes insipidus are associated with different

TABLE II

Type of Tumor	Acromegaly		Fröelich's Syndrome		Polyuria	
	Present	Absent	Present	Absent	Present	Absent
Struma—all types	14	18	8	24	0	28
Adenoma—all types	37	40	10	58	3	55
Carcinoma	2	9	5	6		
Cranio-pharyngeal Duct Tumor			14	20		
Sarcoma	7	20	9	18	2	25
Endothelioma			3	2		
Teratoma			1	8		
Metastatic Tumor			2	1	11	4
Totals	60		52		19	

types of enlargements and tumors of the hypophysis. The great majority of cases of acromegaly were associated with strumas or adenomas that were rich in eosinophil cells.

Malignancy in tumors of the hypophysis manifests itself chiefly by the manner and extent of its invasion of the capsule and adjacent tissues. They sometimes erode and grow into the sphenoid bone, and even invade the roof of the pharynx or the orbit. They may spread out over the surface of the dura mater, or invade the substance of the brain itself. Metastases are exceedingly rare. When they do occur, they are usually within the cranial cavity. Thus Smoler and Stolpe encountered metastases in the brain, and Cagnetto(*a*), in the meninges of the spinal cord in cases of malignant tumors of the hypophysis. I have found in the literature no references to metastases in distant organs. The anterior lobe of the hypophysis is richly vascular, and the tumors which originate from it also contain numerous thin-walled blood vessels. As pointed out by LeCount it is difficult to explain the absence of metastases in sarcomas of an organ that is so copiously supplied with blood vessels. This very absence of metastases casts doubt upon the accuracy of the diagnosis of sarcoma of the hypophysis.

Hyperplasias.—In certain pathological and physiological states affecting other organs of the body, the hypophysis usually undergoes hyperplasia or hypertrophy. The increase in size is distinct but moderate and uniform; and the weight rarely exceeds 1.5 grams. The enlargement takes place in the transverse and vertical diameters, so the first evidence of enlargement of the hypophysis is manifested by a bulging of the dura mater covering the sella turcica. The sella turcica itself is not enlarged and the bones forming it do not undergo pressure atrophy.

Increase in the size of the hypophysis during pregnancy is constant, and has been studied in women by Erdheim and Stumme, Kohn(*b*), Kolde, Kraus(*c*), Siguret, Launnois and Mulon, and others. The enlargement is moderate and uniform. The maximum weight reported by Erdheim and Stumme in their large series of cases was 1.8 grams. This increase in size is the result of the appearance in the anterior lobe of a new type of cell in very great numbers. These cells are large, their nuclei round or oval and not deeply stained, and their cytoplasm contains granules which stain very faintly with eosin. These cells are believed by Erdheim and Stumme to be transformed chief cells; while Kraus(*c*) considers them as variants of the eosinophil cells. They are commonly designated as the cells of pregnancy ("Schwangerschaftszellen"). They are usually distributed rather uniformly throughout the anterior lobe, and among them lie the diminished numbers of eosinophils and basophils. After the termination of pregnancy these characteristic cells largely but not entirely disappear, and the size of the hypophysis again approaches normal. With each succeeding pregnancy, especially if they follow each other at short intervals, the number of cells remaining is augmented. This accounts for the greater average weight of the hypophysis in women who had borne children, as observed by Simmonds(*e*), Erdheim and Stumme, Tölken, and others.

Similar changes in the hypophysis of lower animals during pregnancy have been recorded by Kolde, Berblinger(*b*), Wittek, Schoenberg and Sakaguchi. Berblinger was able to produce in the hypophyses of virgin rabbits and guinea pigs changes characteristic of pregnancy, by the injection of extracts of the respective placenta and fetus.

Castration of animals of both sexes induces, usually, a slight uniform increase in weight and size of the hypophysis; and, quite constantly, distinctive changes in its histologic structure characterized by a marked and uniformly distributed increase of the eosinophil cells of the anterior lobe. These changes have been observed in a large number of different species of animals by Marrassini and Luciani; in cattle by Wittek, and by Schoenberg and Sakaguchi; in guinea pigs and rabbits by Kolde; and in rats by Schleidt. Rössle, in a series of 28 women who had previously undergone oöphorectomy, found that the changes in the hypophysis due to castration consisted in an increase and heterotopy of eosinophils and a paucity of basophils. Kon(*b*) found similar alterations in the hypophysis of a man who had been castrated on account of tuberculosis of the testicle.

Hyperplasias of the hypophysis have been encountered occasionally in myxedema, cretinism and after thyroidectomy. This subject has been discussed in some detail in another paragraph.

Struma Pituitaria.—In this condition there is a uniform enlargement of the entire anterior lobe of the hypophysis due to multiplication of its

cells, and not accompanying any one of the physiological or pathological states with which hyperplasia is associated. The size of a strumatous hypophysis may vary from a slight increase over the normal size up to five or more centimeters in its greatest diameter. The shape is usually oval, and the surface is smooth and regular except where it is subjected to pressure, especially by bone. A struma may cause pressure atrophy of the bone with enlargement of the sella turcica. It usually grows upward in the direction of least resistance, pushing the dura mater before it and pressing upon the under surface of the brain. The larger strumas may also bulge forward and, by pressure upon the optic chiasm, cause bitemporal hemianopsia.

The surfaces made by sectioning a struma of the hypophysis are darker red in color than the normal anterior lobe. The appearance is homogeneous; that is, there are no nodular masses present. The posterior lobe is usually flattened and atrophic but not otherwise changed. A struma is not adherent to the sella turcica; its capsule is intact and not invaded by the cells of the growth.

All of the usual cell types of the anterior lobe are present in a struma; but, as a rule, one type predominates. There are thus, eosinophil cell, basophil cell, and chief or chromophobe cell strumas, according to the type of cell that is present in greatest numbers. The arrangement of the cells is that of the normal anterior lobe, that is, usually in the form of solid cords, occasionally as alveoli. Colloid is usually not abundant. Blood vessels are, ordinarily, numerous and are frequently surrounded by cells with an alveolar arrangement.

It is a question whether a struma of the hypophysis is a true tumor, any more than a struma of the thyroid is a tumor of that gland. It seems more likely that a struma is a hyperplastic, rather than a neoplastic condition—a sort of superhyperplasia.

Neoplasms of the Hypophysis

Adenoma.—These are sharpy circumscribed epithelial growths within the anterior lobe of the hypophysis. Nothdurf has described one such new growth in the posterior lobe. They are spherical or oval in shape, so that on surfaces made by sectioning they appear as round, sharply defined areas, usually lighter in color than the remainder of the anterior lobe. They vary in size from masses too small to be seen upon gross examination up to several millimeters in diameter. The largest in Kraus' (*c*) series of 25 adenomas, measured 6 by 7 mm. These adenomas may be single or multiple. In 6 of Kraus' cases there were two; in two cases, three; and on one case there were five such masses in the anterior lobe. These adenomas, as pointed out by Lowenstein, are almost always in the periphereal portion of

the anterior lobe, and very rarely, if ever, in the central portion. The hypophysis as a whole may or may not be enlarged. The largest hypophysis is Kraus' series of cases measured 3 by 3 by 4 cm. On account of the nature of the lesion the surface of the hypophysis is likely to be irregular in those instances in which the adenoma or adenomas acquire considerable size.

Microscopically, an adenoma is composed of epithelial cells arranged in cords, with occasional alveoli, and having the characteristics of one or another of the cell types commonly found in the anterior lobe. In Kraus' (*c*) series there were chromophobe, transitional, eosinophil, basophil, and pregnancy cell adenomas. The granules in an adenoma are usually less abundant and sometimes stain less deeply than in the corresponding cells of the normal portion of the anterior lobe. They also contain less fat and lipoids than those of the adjacent glandular portion. Mitotic figures are only very rarely observed.

Fig. 7. A chief cell adenoma of the anterior part of the anterior lobe of the hypophysis. Magnified 24 times. Its peripheral position is indicated by the capsule of the gland seen in the lower left hand segment.

The adenomatous mass is distinctly differentiated from the surrounding anterior lobe, although frequently there is no definite connective tissue capsule.

It is uncertain whether these circumscribed masses are truly neoplastic in nature, or are, rather, a definitely localized hyperplasia similar to the nodules found in struma nodosa of the thyroid (v. Gierke). These adenomas are not uncommon in persons over 40 years of age. In Kraus' series of 25 cases, only 3 were under 30 years of age, while only 6 were less than 40 years old.

Carcinoma.—Neoplasms which originate in the anterior lobe, break through the capsule and infiltrate the adjacent tissues, and even erode and invade the sphenoid bone, are occasionally met with. These tumors possess all of the criteria of malignancy except the production of metastases at a distance from the primary tumor. Most of the cases reported in the

literature as malignant struma or malignant adenoma might more correctly be classified as carcinomas.

Carcinomatous growths of the hypophysis may reach considerable size, the largest of which I found record measured 6 by 4 by 7 cm. They invade the capsule of the gland; become adherent to the adjacent structures; erode bone and grow into the openings thus made; and their surfaces are irregular and nodular.

The histologic structure of a carcinoma of the hypophysis is atypical. The cells are no longer arranged in the characteristic cords, or groups, or acini; but are more closely and irregularly packed together with scant stroma between the cell masses. The cells are chiefly chromophobic in type, but by the employment of special stains, granules can be demonstrated in some of them, thus indicating the epithelial origin of the tumor. Those cells which surround the blood vessels are frequently cuboidal or cylindrical and are placed radially about the vessel, an arrangement which led Moskalew to apply the name "epithelioma telangiectoides" to a carcinomatous growth of the hypophysis. The histologic structure may vary in different parts of the tumor mass, as noted by Strada, Hippel, and Ribbert. Often that portion of the tumor which breaks through the dura mater and grows diffusely is more atypical in structure than the intrasellar part. An explanation of this may be that the portion which remains in the sella turcica represents the remains of the normal portion of the gland which has become more or less invaded by the carcinomatous cells. For it is no more likely that all of the cells of the anterior lobe of the hypophysis simultaneously become cancerous than that all of the cells of the breast acquire malignant characteristics at the same time. So small an organ as the hypophysis can quickly become thoroughly infiltrated with the new growth.

In the most atypical forms of carcinoma of the hypophysis, the tumor may lose all distinguishing characteristics of hypophyseal structure. The cells become so completely dedifferentiated that they may resemble small round cells, or even, perhaps as a result of mutual pressure, spindle cells. It is only by the finding of a few granules in occasional cells in specially stained preparations that these tumors can be differentiated from sarcomas and correctly classified.

Sarcoma.—The occurrence of sarcoma of the hypophysis is possible, but it appears probable that the majority of those cases reported in the literature as sarcomas were, in reality, the most atypical and most malignant form of carcinoma. Until cases are reported in which the diagnosis is proven beyond question by the use of special granule stains, there is little to be learned from a study of the cases recorded in the literature as "sarcoma of the hypophysis." In the 38 cases so diagnosed which I have collected almost every type of sarcoma is included except the giant cell type. Round cell sarcoma was the diagnosis which appeared with the greatest frequency.

Before a diagnosis of sarcoma of the hypophysis is made a very thorough examination should be made of sections especially stained to bring out the intracellular granules.

Tumors Arising from "Rests" of the Craniopharyngeal Duct.—Erdheim(*b*) has described a very definite type of tumor in the region of the hypophysis which develops from rests of the embryonic craniopharyngeal duct. Along the anterior surface of the infundibulum there is a thin layer, or tongue-like process of cells extending upward from the anterior lobe. This process ends high up on the infundibulum in an "end-swelling," which in about eighty per cent of adults contains small groups of squamous epithelium. There are similar small groups of squamous cells on the front surface of the anterior lobe at the place of attachment of the infundibular process. Such squamous cells are not found elsewhere in the anterior lobe. The tumors described and differentiated by Erdheim originate from one or the other of these two groups of squamous cells. Their location, and their gross and microscopic appearance are characteristic and pathognomonic.

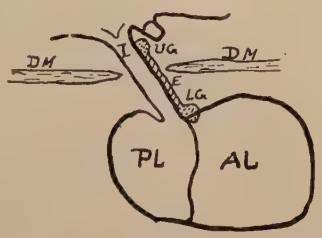


Fig. 8. Schematic drawing to indicate the origin of craniopharyngeal duct tumors. AL. Anterior lobe. PL. Posterior lobe. I. Infundibulum. E. Extension of cells of anterior lobe upwards on front surface of the infundibulum. UG. Upper group of squamous epithelial cells. LG. Lower group of squamous epithelial cells. DM. Dura mater.

These tumors vary somewhat, depending upon whether they are benign or malignant, and whether they originate from the upper or the lower groups of squamous epithelial cells. All of them lie behind the optic chiasm, below the brain, above the hypophysis, and within the circle of Willis.

(1) If the tumor develops from the upper group of cells and is benign, it is composed of one or more simple papillary cysts, usually filled with clear fluid; and is separated from the hypophysis by the dura mater covering the sella turcica. Malignant tumors originating from this source are solid; they invade and push upward the floor of the 3d ventricle of the brain; invade the dura mater covering the sella and compress the hypophysis.

(2) A benign tumor originating from the lower group of squamous epithelial cells appears as a cystic new growth lying below the dura mater which it pushes upward. It flattens the hypophysis and is attached to its surface. It may erode the bones at the base of the skull and even bulge into the vault of the pharynx. If the tumor developing from this lower group of cells is malignant, it first grows in the sella turcica as a solid mass, invading and compressing the hypophysis; it erodes the bone; and grows through the dura mater and infiltrates the under surface of the brain.

Histologically, these tumors resemble adamantinomas, the similarities

to which have been especially emphasized by Ehlers. They are distinctly squamous cell tumors. The peripheral cells, both of the cysts and of the solid masses, that is, the cells which rest upon the basement membrane, are columnar like those cells composing the columnar cell layer of the skin and mucous membrane of the mouth. In the deeper layers, the cells show the connecting bridges—"prickle cells"—of the stratum spinosum of the mucous membrane of the mouth and the skin. True cornification does not occur, although hyaline degeneration of the central parts of some of the masses may give rise to structures which somewhat resemble epithelial "pearls." The absence of cornification is a characteristic, which, according to Erdheim(*b*), differentiates these tumors sharply from cholesteatomas that may originate in the same region, but whose origin is not connected with the hypophysis.

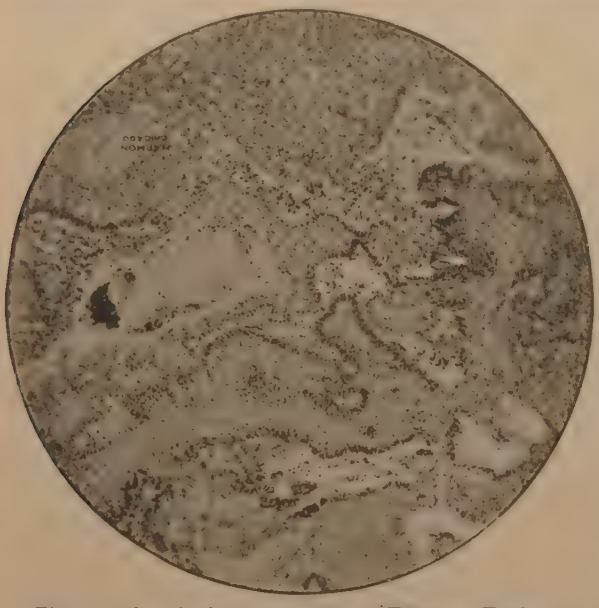


Fig. 9. Craniopharyngeal Duct Tumor (Erdheim). Magnified 110 times. Reproduced from article by Dr. Harry Jackson, Jour. Amer. Med. Assn., 1916, lxvi, 1082.

Craniopharyngeal duct tumors are very frequently accompanied by Fröelich's syndrome. In the series which I have collected, this symptom complex was present in 14 out of some 34 cases in which a statement was made concerning its presence or absence.

Endothelioma.—Seven cases diagnosed as endothelioma of the hypophysis have been found in the literature, including a tumor reported by Wolf as a cylindroma. It is not clear in all cases whether the tumor actually originated in the hypophysis or invaded the gland. In Zak's case the hypophysis was intact but compressed by the tumor. In those of Rennie and Mullaly(*b*) the hypophysis had been almost completely replaced by the new growth. Schoenemann records a case of lymphangioma of the hypophysis which is contrary to Thaon's(*b*) view that the hypophysis is lacking in lymph vessels, if, indeed, Schoenemann's tumor actually originated in the gland.

Diagnosis of perithelioma has been found seven times. Only those of Jackson(*a*) and of Kon(*b*) are described with sufficient clearness.

Kraus(*c*) mentions "perithelioma-like structures" in two hypophyses which also contained adenomas. The peritheliomas described by Jackson and by Kon were characterized by masses of cells with small round nuclei, arranged around blood vessels from which they were separated by a narrow hyaline zone.

Psammomas of the hypophysis have been recorded by Woollcombe and by Windenberg.

Teratomas, closely associated with the hypophysis, have been reported nine times. These have usually contained bone, cartilage, connective tissue, and, sometimes, squamous epithelium. White found a teratoma of the hypophysis containing medullated nerve fibers, striated muscle, connective tissue, fat, and a structure resembling a sympathetic ganglion.

Tumors of the Pars Intermedia.—These are very rare. Boyce and Beadles(*b*) found, somewhat accidentally in the routine examination of hypophyses, a small mass on the infundibulum, having the structure of the middle lobe of the hypophysis. There were no symptoms that could be ascribed to the presence of the tumor. Erdheim(*b*) observed a similar mass the size of a hemp seed in the infundibulum. A tumor at the base of the brain described by Cushing(*b*), compressed the anterior lobe of the hypophysis, and was composed of vesicles containing colloid. There was undoubted evidence that the tumor originated from the pars intermedia. Schmorl found a distinct hyperplasia of the middle lobe in a case of myxedema. Weichselbaum found a group of colloid cysts lined with ciliated epithelium in the back part of the anterior lobe.

Rare Tumors of the Hypophysis.—A lipoma of the posterior lobe has been described by Weichselbaum. Arnold(*b*) reported a lymphadenoma of the anterior lobe in a patient with acromegaly. Stains to show granules were not used, and it may be justly questioned whether this was not in reality a struma pituitaria. Gliomas of the neurohypophysis have been recorded by Nonne(*b*), Hilario, and Burr.

Erdheim(*d*) has described a remarkable tumor, composed of eosinophil cells like those of the anterior lobe of the hypophysis, and occupying the sphenoidal sinus. The hypophysis was in its usual position in the sella turcica and was normal in appearance. The patient was acromegalic. Leegaard removed at operation a large soft tumor from the roof of the pharynx. Histologically, the growth resembled the anterior lobe of the hypophysis, and probably developed from rests of the "hypophysis pharyngea." It is possible that in cases of acromegaly with normal hypophyses, exploration of the sphenoidal sinuses and of the vault of the pharynx, might reveal a tumor composed of hypophyseal cells.

Metastatic Tumors of the Hypophysis.—Metastatic tumors in this organ are not common. In 1,500 necropsies of all kinds Simmonds(*f*) observed this lesion 17 times. In 40 cases of carcinoma that came to autopsy Fraenkel(*a*) found metastases in the hypophysis twice. In 20

recorded cases (McCarthy and Karsner, Haman, Wolf, Berblinger(*a*), and Merkel, each one case; Fraenkel, 2 cases; Simmonds(*c*), 5 cases; Schmorl, 8 cases), in which data were given, the primary tumor was in the breast 6 times; in the thyroid gland, 3 times; in the bronchi or lungs, 3 times; in the floor of the third ventricle of the brain, twice; and once each in the esophagus, prostate, and the skin about the ear. All of the primary tumors were carcinomas except the two in the base of the 3d ventricle, which were sarcomas. The metastatic tumors of the hypophysis are usually small. That reported by Wolf, however, was the size of a hen's egg. In 12 cases the metastatic tumor was in the posterior lobe; in 2, in the neurohypophysis and pars intermedia; in 3, in the anterior lobe; in 2 instances the entire gland was involved; and in one, the tumor was limited to the pars intermedia and infundibulum. Of these 20 cases, 11 showed polyuria. One patient was very obese, and one was emaciated.

Cysts of the Hypophysis

Necrosis of the central portions of a tumor of the hypophysis may produce a cyst-like cavity filled with fluid. Most frequently the cysts of the hypophysis are benign cranio-pharyngeal duct tumors. These cysts may be small or large, single or multiple, and may have walls that are smooth or, more often, studded with papillary growths. They are lined by stratified squamous epithelium. After middle age, small colloid-filled cysts are found almost constantly in the pars intermedia. Occasionally such cysts may acquire considerable size.

Animal Parasites in the Hypophysis

Soemmering observed an echinococcus cyst, with 15 echinococci, in the hypophysis. Roger reported the case of a 13-year-old boy in whose sella turcica he found an echinococcus cyst containing 59 grams of fluid. Kufs(*b*) has recently described a case of cysticercus meningitis, with a cysticercus cyst of the hypophysis the size of a pea.

Widakowisch found a nematode worm, which he was unable to identify, coiled up in the posterior lobe of the hypophysis of a cat. This portion had been almost totally destroyed by the parasite. No clinical data as to the degree of adiposity or the presence of polyuria were recorded. Widakowisch believed that the worm probably reached the hypophysis from the ventricles of the brain through the infundibulum.

Acromegaly . . . . . *Peter Bassoe*

Definition and Clinical Conception—History of the Development of the Conception of Acromegaly—Etiology—Clinical Picture—Congenital Acromegaly—Onset in Childhood—Primary Symptoms and Lesions—Skeletal Changes—General Features of Conformation of the Body and of the Skeletal Changes—The Skin and Its Appendages—The Muscular System—The Upper Respiratory Tract—The Circulatory System—Metabolic Disturbances—The Genital System—Associated Endocrin Disturbances—Psychoses—Secondary Symptoms and Lesions—Differential Diagnosis—Prognosis—Treatment.

Acromegaly

PETER BASSOE

CHICAGO

Definition and Clinical Conception of Acromegaly

The term acromegaly was constructed by Pierre Marie(*a*) in 1886 to designate *"a peculiar, non-congenital hypertrophy of the upper, lower, and cephalic extremities."* It literally means "large ends." Marie's conception was purely morphological and based on external appearances. At the time of his first formulation of this morbid entity—he felt that it was one —he did not know its relation to the hypophysis, or the tremendous impetus its study was to give to pathology, especially to research directed to the ductless glands and the skeleton. Minkowski, in 1887, was the first to suggest the probable rôle of the hypophysis but many years elapsed before there was any clearness as to *how* this rôle is played. According to our modern conception *acromegaly is a morbid state caused by glandular hyperplasia and functional overactivity of the hypophysis, resulting in*: (*a*) *primary glandular symptoms consisting mainly of abnormal growth of the soft and bony parts of the "end segments"—tongue, jaw, hands and feet;* (*b*) *secondary glandular symptoms from associated and subordinate disturbances of other endocrin glands, notably of the gonads, the adrenals and the thyroid;* (*c*) *local mechanical pressure symptoms caused by the hypophyseal tumor and affecting chiefly the optic chiasma and nerves;* (*d*) *secondary and general brain symptoms dependent on increased intracranial pressure.*

History of the Development of the Conception of Acromegaly

Marie's announcement in 1886 met with immediate approval and a spontaneous response from medical investigators everywhere. His description was based on two personal cases and a few selected from the literature, previously described under various titles. Cases multiplied with marvelous rapidity. The thesis by Marie's pupil, Souza Leite, in 1890,

contained an account of 38 cases. In 1891 Duchesneau added 28, and in 1892 Collins brought the number up to 83.[1] The old medical literature was ransacked, and old paintings and sculpture scrutinized. Apparently the oldest find was that by Sternberg of a life size portrait dated 1553 in a castle in Tyrol of a "giant" at the court of Frederick II, elector of the Palatinate, showing the typical features of acromegaly. The oldest medical description appears to be one by Saucerotte in 1772, to whom also is to be credited the first museum specimens of acromegalic bones which he secured from the grave of his patient. They are preserved in the Musée Dupuytren in Paris. In 1839 Magendie gave a vivid description of two women under his care in the Hôtel Dieu in Paris.[2] The skeletal changes had been described in detail by Langer in 1872. He noted the huge lower jaw, the large sinuses, the bony enlargement at the points of muscular attachment and from the enlargement of the sella turcica he inferred that the hypophysis had been diseased. In Italy, Vergo in 1864 gave the postmortem findings, which included enlarged sella and tumor of hypophysis, in a case which he recorded as an instance of "prosopectasia," a term also used by Taruffi (1879), who described an acromegalic skeleton in the museum at Bologna. Brigidi (1887) described the postmortem findings in an Italian actor with "strange deformities," and, according to Sternberg, gave the first histologic description of the hypophysis tumor in acromegaly. Both Taruffi's and Brigidi's cases are accepted as typical instances of acromegaly in the thesis of Souza-Leite. In England, Cunningham (1879) described an undoubted case of acromegaly and diabetes; the skeleton of the patient was preserved and described, in the light of Marie's announcement, by Thomson in 1890. In Germany, Fritsche and Klebs in a monograph published in 1884 gave an excellent description of the acromegalic giant, Peter Rhyner, and in France, Henrot, in 1877, had described a case which he considered one of myxedema.

In view of such a large number of early cases the failure to correlate them prior to 1886 is only explainable by their having been reported from widely separated localities, under very varied titles, and partly in obscure publications. Since the earlier collective reviews previously mentioned, the literature on acromegaly has grown tremendously. An excellent collective review by Sternberg(*a*) appeared in 1897. The most important re-

[1] All references to and including 1898 are found in the exhaustive articles by Harlow Brooks and Hinsdale. The first case reported in America was that of a woman presented before the New York County Medical Association on October 15, 1888, by Isaac Adler and described by him in greater detail the following year. The necropsy report of this case is found in the article of Brooks ten years later. J. T. O'Connor also reported a case in 1888.

[2] "One is a real female monster. Head, extremities, trunk, all are of enormous volume. Her tongue is broad like that of a calf, her fingers as wide as four of mine. Her voice is like a man's, full and deep; I do not doubt that her larynx also is hypertrophied. The other woman is similar, but on a smaller scale. Being younger, and growing more rapidly from day to day, I do not doubt that she will soon rival her senior. Nothing explains the enormous growth in these two women."

cent single contributions are found in the monographs on the hypophysis by Cushing(*b*) and by Blair Bell(*b*), and in the text books on the organs of internal secretion by Falta(*c*) and by Biedl(*b*). A unique contribution is the self-description by Dr. Mark, an English physician and a victim of the disease. He relates the subjective symptoms and mental attitude of the patient in a delightful manner and with a vividness possible only from one with personal experience and possessed of medical acumen.

Etiology

The disease occurs in all races and climates. The sexes are about equally affected, the female possibly predominating slightly (Léri, Bell). Of 210 cases collected by Sternberg, 104 were in men and 106 in women, while of Hinsdale's 130 cases the numbers were, respectively, 73 and 57. The age at the onset, in the majority of cases, is between 20 and 30 years; in a fair number between 30 and 40, and in a few instances between 15 and 20 and after 40. Onset in childhood or evidence of the disease at birth is exceptional and the cases reported are largely debatable. They will be analyzed on a subsequent page where it will be shown that most of them are complicated by other endocrin affections or by congenital syphilis.

Fig. 1. Acromegaly in father and daughter. (Franchini and Giglioli.)

a. Heredity.—Heredity plays no important rôle though it has been recorded in a few instances. Fraenkel, Stadelmann and Benda report a case of typical acromegaly in a man whose brother probably had the same disease, and the father and a sister are said to have had similar deformities of the face and extremities. Bonardi reports acromegaly in father and son; Franchini and Giglioli in father and daughter. Schwoner and Fräntzel each report cases in mother and daughter but only on hearsay evidence in the case of the daughters, and even the mother in Fräntzel's

report is considered by Marie a case of pulmonary hypertrophic osteoarthropathy and not acromegaly. Machwitz briefly mentions acromegaly in the 18-year-old son of an acromegalic and diabetic father of 46. H. Salomon's fourth patient, a woman of 51 with typical acromegaly and diabetes, also reported by Schäffer, had a mother who probably suffered from both of these diseases during the last four or five years of her life. Cyon reports the disease in three sisters and Leva in two cousins. Cushing's(*b*) case XXXI, a male acromegalic of large size, had a giant maternal grandfather and his own three children were unusually large at birth. M. T. Craft, a proven case of acromegaly, in his description of his own case states that the giant Bates (see paragraph on heredity in gigantism) was his paternal grand uncle. Goiter and diabetes in relatives are not infrequently mentioned, as is myxedema. Pope and Clarke described and pictured an acromegalic father and myxedematous daughter. The patients, themselves usually tall, often come of families made up of people above average size.

Pregnancy.—As Erdheim and Stumme have proven the existence of a physiological enlargement and overactivity of the hypophysis during pregnancy, it is not surprising that actual acromegaly occasionally is reported as commencing during pregnancy. Marek reports as "pregnancy acromegaly" the case of a woman of 28 years during both of whose two pregnancies typical symptoms—enlarged nose, fingers and toes, inability to approximate the teeth—developed and later subsided. Fehr reports an instance of bitemporal hemianopsia without other signs, developing during pregnancy and remaining stationary for ten years though the sella was much enlarged (21 mm. long). In Cushing's case XXIV, that of a woman of 37 with 8 pregnancies, a tendency to enlargement of the hands and feet was noted during three pregnancies prior to the establishment of the disease. On the other hand, Goldstein(*b*) reports the development of acromegaly within a year after removal of the uterus and adnexa for myomata. This woman was of a coarse build so a predisposition was thought to exist.

Acute Infections.—Cushing records previous pulmonary infections and typhoid in some of his cases and comments on the tendency to rapid growth following an attack of the latter disease in a young subject. In one of his cases the onset coincided with that of tuberculosis of the cervical glands. Others have reported acromegaly as developing after typhoid fever (Hecht, Messedaglia, and others), but most probably these are mere coincidences, and the same is true of the cases reported as following alcoholic excesses, coal gas poisoning, etc.

Trauma.—While basal skull fracture has been shown to have caused symptoms of hypopituitarism with adiposity, probably from lesion of the posterior lobe (Madelung, Cushing) the rôle of head injuries in connection with acromegaly, although several times alleged, cannot be considered

at all proven. Bleibtreu's case of acromegalic gigantism following trauma and showing at necropsy destruction of the hypophysis by old hemorrhage is unique and difficult to interpret.

Fright is frequently mentioned as having preceded the onset, apparently only in female cases. Pel(*c*) has observed three instances and is convinced that it should be accepted as an etiologic factor, supporting himself on analogous claims made in connection with Graves' disease and diabetes. One of his patients, however, was pregnant at the time of the fright.

The Clinical Picture of Acromegaly.

If the facts stated in our definition are borne in mind it will be easy for the reader to become oriented in regard to the complex and unusual symptomatology. In order to be an acromegalic it is necessary for a person to have had at one period or another of his life a state of overactivity of the anterior lobe of the hypophysis. A certain train of symptoms accompanies this active stage: headache of a "pituitary" type, lowered sugar tolerance and tendency to glycosuria; accentuation of secondary sexual characteristics in the case of the male, and acquisition of certain male characteristics in the female; finally the permanent enlargement of the "acra" (nose, lips, lower jaw, hands, feet). The active stage may last only a few months but the patient is indelibly marked as an acromegalic for the rest of his life. From the mere external appearance of the patient we cannot tell whether the case is an active or a quiescent one, an instance of primary hyperpituitarism or one of secondary glandular overactivity as the result of nature overreaching herself in an attempt to correct a primary glandular deficiency which in turn may have been but part of a complex ductless gland disorder. This is well brought out by Timme(*a*) in his description of a "new pluriglandular compensatory syndrome" with four stages, the first in childhood and largely due to endocrin deficiencies, the second at puberty with certain eunuchoid features, including rapid skeletal growth and deficient sexual development. In the third stage, between the ages of 20 and 30 years, general gigantism or acromegaly may set in, and the sella turcica becomes enlarged. The fourth stage is one of arrest with persistence of the morphologic acromegalic features, or of progression, depending on whether or not compensation has become established. The cases of pituitary disturbance in young people, described by Beverley R. Tucker, with especial attention given to mental disturbances, are instructive since those reported as "preadolescent hyperpituitarism" showed an acromegalic trend and in them evidences of pluriglandular disturbances existed. Thus, the first patient, a woman of 26 years, had fully developed breasts at nine years, menstruated at 11 years, and at 15 her entire arms were covered with hair. The cheek and jaw bones were promi-

nent, and the sella turcica was enlarged. The patient began to show morbid hypersensitiveness at 12 years, with varying moods, and hallucinatory episodes. Tucker's second patient had a similar precocious development, mental symptoms of exaggerated hysterical type, enlarged sella and hypertrichosis, but otherwise no feaures of acromegaly. To Cushing, however, belongs the chief credit for clarifying our views. In his masterly monograph based on an unequaled array of carefully observed and brilliantly analyzed cases of all kinds of pituitary disease he, first of all authors, has given a true perspective and showed with unerring logic that the morphologic entity, acromegaly, is the end result of anterior lobe hyperfunction of long or short duration, with or without admixture of symptoms produced by previous or subsequent hypophyseal hypofunction, disorder of other ductless glands, pressure upon or erosion of neighboring brain structures, and symptoms of increased intracranial pressure caused by the purely mechanical effect of the hypophyseal tumor. Cushing, Oppenheim, and Heinicke have shown that hyperpituitarism and the *syndrome* acromegaly may be produced by hydrocephalus (secondary to cerebellar tumor in the cases of Cushing and Oppenheim).

With this precision of our view of the syndrome of acromegaly as the morphologic expression of a past or persistent state of hyperpituitarism we are prepared to view the various features in greater detail without losing our bearings. Many apparent contradictions in earlier descriptions are due to the failure of the authors to distinguish between active and quiescent, primary and secondary states, between glandular, neighborhood, and general pressure symptoms.

General Description.—The early symptoms generally consist in a changed appearance of the features which become coarse on account of thickening of the nose and lips, enlargement of the tongue and lower jaw, and prominence of the superciliary ridges. The skin and subcutaneous tissues are thicker, often the skin is darker, rougher and thrown into folds. The hairiness of the body increases. This is particularly conspicuous in women, who may develop a heavy growth of dark hair between the breasts, and on the abdomen and legs, and sometimes also a beard such as more frequently is seen in very old women. In women the coarseness and huskiness of the voice and a general tendency to a masculine conformation of the body are noted. Amenorrhea is an early feature while in men a period of increased sexual activity frequently precedes the later almost constant decreased sexual power or impotence. Following enlargement of the lower jaw the hands and feet increase in size, generally more conspicuously in width than in length, and, as shown by röntgenologic examination, the enlargement is chiefly of the soft parts, though later a decided bony hypertrophy may follow. While the hands and fingers usually are notably broad, Marie early recognized a type of elongated hand as well.

Among the early subjective symptoms headache, pain in the face, and

paresthesias in the head and face usually predominate. Mark, from personal experience, says that they exert a constant, all pervading influence on the life of the patient and constitute his most serious handicap in the struggle for existence. He describes a sensation as if the face were in a vise, as if the antrum were tightly packed, the teeth too large for their sockets and the eye pressed upon. Sensitiveness to light and to wind striking the face was marked in his case. The headache, described as deep seated and "splitting" by Mark, is often located deep in, between the temples, and corresponds to the recently described "pituitary headache" (Pardee, Cushing), thought to be caused by distention of the dural envelope of the pituitary gland. The latter, as Pardee points out, is entirely surrounded by a firm framework, on three sides by bone, above by dura, and only on the lateral aspect is there any opportunity for expansion. The patient will often place his fingers on either temple, point directly to the hypophysis and say the headache is "between here." Characteristically enough, these headaches in the rather larval pituitary or multiglandular cases described by Pardee were frequently attended by other symptoms familiar in typical acromegaly: a sense of fatigue, yawning, mental depression, and his female patients showed a tendency to mustache and a masculine type of pubic hair and enlargement of the bony framework.

For a brief time there may be a feeling of increased strength commensurate with the enlarged frame but soon a feeling of lassitude and an inaptitude for work and exertion supervene. What Mark so well describes as the "acromegalic state" into which he passed at intervals consists of a feeling of fatigue, as of being partly under an anesthetic, a desire to keep absolutely still, intolerance of noise and of strong light, a dizzy feeling, dyspnea on exertion, a loss of interest in everything. Mental depression and general discouragement are pronounced and may lead to actual melancholia with suicidal trend. Polydipsia, polyuria and glycosuria are common during the periods of active disease, as is increased sweating. When the hypophyseal tumor enlarges and breaks out of its sellar confinement the "pituitary type" of headache may be relieved, to be replaced in the event of further growth of the tumor by the ordinary brain tumor headache, sometimes accompanied by vomiting, dizziness, and epileptiform attacks. Pressure on the neighboring chiasma leads to optic atrophy, visual impairment, with characteristic distortions of the visual field,—notably bitemporal hemianopsia. Anosmia may result from involvement of the olfactory bulbs. Exophthalmos is occasionally observed and usually attributable to fatty deposits or bony changes in the orbits, or to compression of the cavernous sinus.

In the late stages cessation of active pituitary symptoms may be accompanied by definite signs of posterior lobe deficiency, such as adiposity and increased sugar tolerance. This has been thoroughly demonstrated by Cushing(*d*) who found such signs in 11 out of 14 cases of acromegaly

(1913). The conditions may even approach the "hypophyseal cachexia" described by Simmonds(*b*) in connection with destructive lesions of the gland such as embolic softening following childbirth, metastatic carcinoma, and tuberculosis. It is characterized by premature senility, general cachexia, loss of pubic and axillary hair, dry, thin, wrinkled skin (Reiche; Schlagenhaufer; Bostroem). In an old case of acromegaly in a man of 61 years reported by Dunn obesity and increased sugar tolerance developed, and also the rare complications of transient edema of the eyelids and transient hemoptysis, the latter ascribed to hemorrhagic edema of the lungs.

Congenital Acromegaly

Marie defined the disease as "non-congenital," and as yet no certain case of congenital acromegaly has been reported. Sometimes a baby presents a multitude of deformities which may be so combined as to produce a resemblance to acromegaly. Such a case is reported by Schmincke who, however, does not consider it one of acromegaly. This baby was 76 cm. long at death at 14 months. The hands and feet, fingers and toes, were abnormally long; kyphoscoliosis was present. The hypophysis was placed deeply in the sella and somewhat flattened but it was normal histologically. Tower skull, talipes, dislocated lenses and other deformities were present. The only case which seriously suggests congenital acromegaly is the following which fortunately has been very well described:

Salle's much discussed case is that of a male child first examined when one day old, when his length was 56 cm., and weight 3125 gm. The circumference of the head was 35 cm. The face was coarse and wrinkled with very large nose and prominent chin. The tongue was very large. A congenital heart lesion was present. The arms and legs were relatively a little longer than normal while the hands and feet were of entirely disproportionate length. The hands were 7.5 cm. long, the feet 10.6 cm. The middle fingers measured 4.5 cm. and the big toes 3.4 cm. The extremities were not thickened but on the contrary very slender. On röntgenologic examination the chief differences from the appearance of a normal child of the same age were the complete development of the center of ossification in the terminal phalanx of the little toe while that of the cuboid was lacking. The Wassermann test was negative and there was no clinical evidence of syphilis. The child had much digestive disturbance and cyanosis and died at the age of 2½ months. The body was poorly nourished; length 59 cm. The feet measured 10.8 cm. and the middle fingers 4.75 cm. The most striking postmortem finding was a decided widening of the sella turcica. The hypophysis was pressed against the back of the sella by a bean-sized growth of bony hardness. The brain was of normal appearance. There was no definite histologic change in the hypophysis although the

number of eosinophile cells was large. The proximal epiphyses of the first phalanges of the second and third toes showed the presence of centers of ossification and the same was true of the epiphyses of the terminal phalanx of the big toe. According to Wilms and Sick these centers normally develop between the third and fourth years.

In discussing the diagnosis Salle excludes pure gigantism on account of the disproportionate hands and feet, and the complete symmetry of the enlargements excludes localized gigantism. The *ostéo-arthropathie hypertrophiante pneumique* of Marie (secondary hyperplastic ostitis) is excluded as the characteristic changes of the periosteum and articular ends of the bones were lacking. As the most probable diagnosis he considers a combination of gigantism and acromegaly or a modified form of acromegaly. Against acromegaly speaks the absence of thickening of the soft parts of the extremities but in addition to the usual *type en large* Marie has described a *type en longue* to which this corresponds. The hypophysis which measured 11x10x4 mm. was of a size corresponding to that of an adult rather than that of an infant. Although no typical hypophyseal adenoma was present the prominence of the eosinophile cells was suggestive of hyperpituitarism.

Warda's mention of apparent congenital acromegaly in the four-year-old child of an acromegalic and possibly syphilitic father is merely suggested by a photograph and not based on personal examination of the child.

A more plausible case is that of Cenas of a boy of fifteen years who was born with asymmetry of the face and developed deformities of the hands when a few months old. At four years he had pigmented spots on the hands and feet, which continued to enlarge so that at fifteen they were described as "enormous." The lower jaw was enlarged and kyphosis was present.

Moncorvo described a microcephalic, idiotic child of fourteen months with enlarged hands, feet, nose, and lips. Hinsdale mentions it as "a case of what seems to be congenital acromegaly," which, however, cannot be considered proven.

Onset in Childhood.—The occasional appearance of *true acromegaly in childhood* is of great theoretical interest, as, according to views now quite current, hypophyseal hyperfunction setting in before the closure of the epiphyseal lines leads to general giant growth rather than to acromegaly. This phase will be discussed in the chapter on Gigantism. It is interesting to pass in review the reported cases in connection with which more or less definite claims for the onset of acromegaly in childhood have been made. In several the data are insufficient. In others we are impressed by the many signs of a pluriglandular affection, the hypophyseal disorder and resulting acromegalic features constituting only a part, though generally the most conspicuous part, of the clinical picture. Field describes a

boy, 17 months old, whose legs began to enlarge at 7 months, then the face, the lower part of which was disproportionately large. The malar bones were prominent and the lips, but not the nose, were large. The hands and feet were very large. There was no röntgenologic examination. Pel(*b*) described a boy of 16 years, with limbs large from birth which continued to grow more rapidly than the trunk, especially after an acute illness at 13. The head, lips and lower jaw were rather small, the genitalia infantile, pubic and axillary hair absent, sella not enlarged. Poor muscular development, increased tendon reflexes and diminished pain sense in the legs suggested to the author the possibility of a complication with syringomyelia. The boy was 172 cm. (5 ft. 8 in.) tall at 16 years. The growth disturbance is evidently largely explained by the eunuchoidism present. A multiglandular disorder also existed in the well studied case of Schultze and Fischer. A girl at 11 years developed headache, vomiting, enlargement of the head, hands and feet, and salivation at the paroxysms of headache. When observed shortly before her death from increased brain pressure at 15, she had not yet menstruated. The head was typically acromegalic. The skin was pigmented and there was heavy growth of hair along the median line of the abdomen below the umbilicus. The necropsy brought out the polyglandular affection: large adenoma of the hypophysis, colloid goiter, persistent thymus, hypoplasia of the internal genitalia. As an additional acromegalic feature there was found a general enlargement of the viscera (splanchnomegaly). Onset with enlargement of the face at 11 years was also noted in Hoppe's second case. There gradually developed hyperostosis of the upper and lower jaws, frontal and temporal bones and the septum of the nose. There was no enlargement of soft parts, or of the hands and feet. The left eye was prominent, and optic atrophy was present. During life a diagnosis of leontiasis ossea was made but after death from a sudden subdural hemorrhage at fifteen there was found, in addition to cranial hyperostosis, an unusually deep sella turcica containing "a large hypertrophied pituitary gland." Hoppe remarks that this finding "strengthens the contention that perhaps leontiasis ossea is a form of acromegaly, but throws some doubt on the contention that pituitary hypertrophy in young individuals leads to gigantism." No histologic description of the hypophysis is given. A fairly clear case of acromegaly in a boy of thirteen years is reported by Babonneix and Paisseau. The face was prominent, with a large, thick nose, and the tongue was of more than twice its normal size. The occipital protuberances and mastoid processes were large. The feet were considerably enlarged, the hands less so. The sella turcica was enlarged. However, an interstitial keratitis was also present which improved on specific treatment, suggesting a complicating congenital syphilis the existence of which may have prevented the expected general giant growth by the presence of syphilitic changes at the epiphyses. Matassaru's case of a child of nine years with characteristic enlargement of the

extremities and tongue and enlarged sella was complicated by myxedema. Claude's case of acromegaly without gigantism, with onset at 15 years, showed signs of hyperthyroidism, and, according to him, possibly adrenal overaction as the blood pressure was increased. The epiphyses in the hands and feet were closed at 18, hence growth in length was impossible. Sicard cautiously uses the term "acromegalism" rather than acromegaly in connection with two brothers, both of whom developed enlargement of the hands at 18 years, later of the feet, and in both there was the unusual feature of such marked enlargement of the tarsal cartilages that the eyes could be only partially opened. In addition to the case previously mentioned Pel(*a*) describes a boy of 16 years, 197 cm. tall, hence to be considered a giant, who in spite of his youth had hands and feet of acromegalic appearance, but there was a suspicion of congenital syphilis since the father had this disease. Hutinel's case of a mentally defective and obese boy of 13 years with large tongue, lips, and feet, and enlarged sella, was probably complicated by syphilis as interstitial keratitis was present, as well as suspicious changes in the teeth and tibiae. Valdes describes a negro boy of 14, with onset at 12 of lassitude and enlargement of the hands, feet and lower jaw. The lower teeth projected beyond the upper. Cervicodorsal kyphosis was also present.

A noteworthy case in a child is that of Franchini and Giglioli, already mentioned in connection with heredity since the father also had acromegaly. At twelve years the daughter began to have headache and became depressed, easily exhausted, drowsy and taciturn. Gradually the face, hands and feet became enlarged. When the patient was observed at fourteen the menses had not yet appeared; the sella turcica was enlarged but there were no ocular symptoms.

Rénon, Dellille, and Monier-Vinard in 1908 described a girl, 16 years old, who developed headache and disturbance of vision at twelve years and then began to grow rapidly, attaining a height of 168 cm. at 16 years. The optic discs were atrophic, the right eye blind. The limbs were disproportionately long. This case was later (1914) reported by Béclère as greatly benefited by X-ray treatment; the headache was relieved, the vision improved and menstruation reëstablished and there was no further progress of skeletal changes.

An interesting group of four cases of acromegaly, all observed after the age of 55 years, but with onset at about puberty, is reported by Schlesinger. In all of them the disease had remained stationary for 40 to 50 years and the patients came under observation on account of other ailments. The first patient, a man of 59, with typical acromegalic features which were present in a photograph taken at fifteen, had a very large heart with mitral and tricuspid insufficiency. The urine contained a large amount of sugar. He had contracted syphilis at twenty and gave a positive Wassermann reaction. The skull was hyperostotic, the sella not enlarged. Ne-

cropsy revealed a cherry-sized adenoma of the hypophysis, syphilitic aortitis, arthritis deformans, thyroid adenoma, hypertrophy and fresh hemorrhages of both adrenals. The second patient was a woman of 63 years, with onset of acromegaly at about 17. She had Argyll-Robertson pupils. Death was from papillary carcinoma of the ovary, and the necropsy also revealed adenoma of the hypophysis. The third patient, a male, 56 years old, had acromegaly from early youth, and came to the hospital on account of lymphatic leukemia. The sella was not enlarged. He was under observation for many years, during which there was no variation in the acromegalic symptoms. The fourth patient, a man of 63, with a diabetic sister, had large hands and feet from childhood. The nose and lips were large. Kyphosis was present and the tibiæ were uneven. The sella turcica was normal on röntgenologic examination. The Wassermann test was negative. The sugar tolerance was not increased. Marked edema of the hands and feet was present and thought to be of the nature of trophedema which rarely exists in acromegaly and is thought by the author possibly to indicate a polyglandular disorder. Ocular symptoms (except early temporary ones in the second patient), headache, and other symptoms of increased intracranial pressure were absent in these cases, and nothing was elicited to indicate that sexual function had been impaired. The author does not state whether any of these patients left offspring. The fact that all of them showed typical changes in the conformation of the face, in the absence of visual impairment and sellar enlargement, confirms the significance of these changes in the face when occurring in youth. It is regrettable that the exact history of the evolution of the disease during childhood and early youth in these cases is not known. They probably belong to the "pluriglandular syndrome," so well described by Timme(*a*), and have passed successfully into the fourth or compensated stage, as thus exemplified by him: "A woman, 33 years of age, with typical acromegaly—hands, feet and skull abnormalities, was admitted for some minor ailment. Her history showed that she began to menstruate at 19 years, had intense headaches at 25 years which for three years resisted all attempts to alleviate, and during whose persistence she began to grow acromegalic. When the headaches spontaneously ceased, the abnormal growth ceased, and she passed an uneventful life to the time of the present slight ailment. Her childhood and adolescence were like those described in the first two stages of this syndrome—fatiguability being the prominent symptom. Her acromegaly, then, was completed at about the twenty-ninth year, did not further increase, and she remained well for twenty-three years longer." C. S. Williamson reports a case in a man of 30 years in whose symptoms there had been no progression for twelve years during which he had gained 90 lbs. in weight.

Climenko and Strauss relate a case at an earlier stage of a similar process. A woman of 22 years had suffered from severe headache for three

years, and the menses had been absent for two years. Within a year her face and hands assumed acromegalic appearances, an abundant growth of hair appeared on the legs and lower abdomen, the latter giving to the pubic hair a male appearance. The breasts atrophied and the buttocks assumed a male contour. The sella was found to be enlarged, with thinning of the anterior and posterior clinoid processes. The color of the face changed from a blond and rosy hue to a dark color with a yellowish reflection, and the skin became rough. This case well illustrates the tendency of the secondary sexual characteristics of the female to change to the male type during "acromegalization" while those of the male become exaggerated.

A series of seven arrested cases, similar to those of Schlesinger, is reported by Hillel. The most striking one is the last case, a man of forty years, with onset at fourteen years and active enlargement of the usual kind until twenty. Then the condition remained stationary. Potency was retained, and he became the father of two healthy children. There were no ocular symptoms. In another man the potency was retained, as was menstruation in four women.

Primary Symptoms and Lesions

The Skeletal Changes

Thanks to the kindness of Dr. Dean Lewis we may introduce the description of the skeletal changes by relating the following case in which necropsy was performed immediately after death and the skeleton subsequently prepared.

A man 40 years old, an inmate of the Illinois Industrial Home for the Blind, was admitted to the service of Dr. Dean Lewis in the Presbyterian Hospital, Chicago, in February, 1913. There was some Indian blood in his ancestry on his mother's side. Eight years previously he had noticed that his head was growing larger as his hats became too small. A year later he had the same experience with his shoes. After another year his vision began to fail. In 1910 he became blind. He presented a very striking picture of advanced acromegaly (see Figs. 2, 3.) with extreme prognathism, immense superciliary ridges, large nose, hands and feet. The skin was very thick and leathery and the hair was thick and course. He measured 6 feet 2 inches in height and weighed 250 lbs. His sugar tolerance was found to be within normal limits. During the following years there was no change in his condition. In January, 1920, he developed pneumonia, was admitted to the service of Dr. W. E. Post in the Presbyterian Hospital and died after an illness of a few days. At the necropsy, held by Dr. B. O. Raulston, a large hypophyseal adenoma was found. It weighed 46 grams. The circumference of the head was 63.5 cm., the

binauricular arc 39 cm., and the distance from glabella to inion 40 cm. The nose was 7.5 cm. long and each nostril 3x1.5 cm. The circumference of the chest at the nipple level was 113 cm., at the costal margin 119 cm., its lateral diameters respectively 38 cm. and 42cm. The circumference of the wrist was 21 cm. on each side. (Fig. 4.) The length of fingers, beginning with thumb, was: right, 9, 8.75, 9.25, 8.25 and 7.5 cm.; left, 8.5,

Fig. 2. Case of advanced acromegaly with blindness. (Case of Dean Lewis.)

Fig. 3. Side view of patient shown in Fig. 2, showing typical kyphosis. (Case of Dean Lewis.)

8, 8.5, 8, 7.5 cm. Length of toes was: right, 12.75, 6.5, 6.5, 6.5, 7.5 cm.; left, 12.5, 6, 6, 7, 7 cm.

Splanchnomegaly was marked, the weight of some of the organs being: heart 620 g., right lung 1840 g., left lung 2136 g., liver 3030 g., spleen 525 g., right kidney 370 g., left kidney, 410 g., right testicle 20 g., left testicle 25 g., right adrenal 20 g., left adrenal 17 g., thyroid 102 g., brain 1496 g. No thymus tissue was found. The length of the small intestine was 34½ feet, of the large intestine 7 feet, and of the appendix 13 cm.

Description of Skeleton.[1]—*The Cranium.*—The cranium is dolichocephalic. All sutures are obliterated. The superciliary ridges are markedly

[1] I am greatly indebted to Dr. D. B. Phemister for most valuable aid in the study of this skeleton.

prominent, forming a smooth, rounded, bony overgrowth which overhangs the superior orbital margin. The external occipital protuberance, the mastoid processes, and the superior nuchal lines also show marked bony overgrowth. The frontal, parietal and occipital bones show hypertrophy which is greatest in their mesial portions, while the squamous portion of the temporal bones and the greater wings of the sphenoid show no hypertrophy and are thinner than normal. (Figs. 9, 10.) The under surface of the base shows marked bony irregularities at the seat of muscular and

Fig. 4. Hand of patient shown in Figs. 2 and 3, as compared with normal hands. (Case of Dean Lewis.)

ligamentous attachments. The canals for nerves and vessels are not reduced in diameter, but the foramen magnum is encroached upon and made irregular by exostoses at its margin. The styloid processes are elongated. A horizontal section of the skull shows thin external and internal tables with marked increase in the thickness of the diploë both posteriorly and anteriorly, and enormous dilatation of the frontal sinuses, the floor of which is formed by the translucent part of the hypertrophic superciliary ridges. The frontal sinuses measures 5 cm. from above downward.

A sagittal section of the vault shows a uniform thickness of 1.5 cm. with thick diploë and thin tables. The internal surface of the vault is

markedly roughened and shows a large number of flattened wart-like excrescences, varying in diameter from that of a pinhead to 1 cm. They are especially abundant along the median line. The vascular grooves are present but somewhat obscured by the hyperostoses.

The base of the skull, from the inside, shows in the anterior fossa slight increase of convolutional markings. The cribriform plate of the

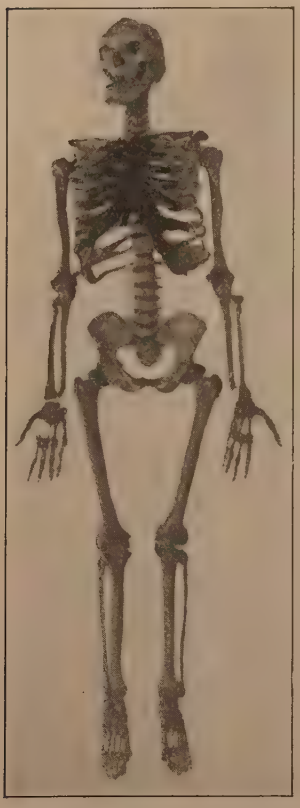


Fig. 5. Front view of skeleton of patient shown in Fig. 2. (Case of Dean Lewis.) Lateral view of skeleton shown in Fig. 4.

Fig. 6. Lateral view of skeleton shown in Fig. 5.

Fig. 7. Skeleton in Osborne's case of acromegaly beside a normal skeleton. (After Osborne, Yale Med. Jour., Dec., 1897.)

ethmoid is small and contains two warty excrescences. The fenestrations on the right side are encroached on by exostoses; on the left side they are little changed. (Figs. 8, 9, 10, 11, 12.) The posterior part of the floor of the anterior fossa is moderately elevated in the median line (from pressure of the enlarged hypophysis).

The middle fossa is markedly altered. Its anterior margin is normal in its lateral portions, but elevated and sharpened in its middle, sellar

portion. Its posterior margin formed by the crests of the petrous bone is markedly irregular and sharpened. The sella turcica is enormously enlarged, measuring 36 mm. antero-posteriorly. The anterior clinoid processes are lengthened, sharpened and displaced laterally, the distance between their points being 45 mm. The middle clinoid processes are completely destroyed. The dorsum sellae and posterior clinoid processes are destroyed except for a small irregular, sharpened ridge at the base. The

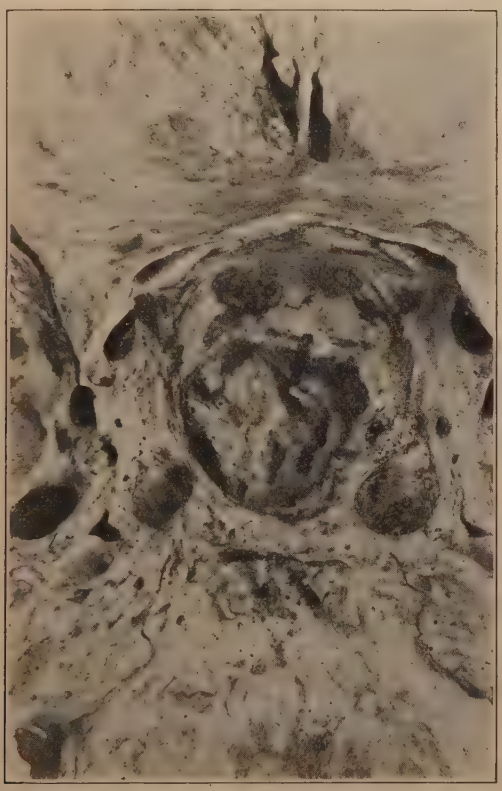


Fig. 8. Region of sella turcica showing bony deposits in its floor and destruction of posterior clinoid processes. (Case of Dean Lewis.)

floor of the sella is entirely destroyed, establishing a communication with the sphenoid sinus. The lateral margins of the sella are entirely eroded. There are two wart-like excrescences of very spongy bone on the anterior sellar wall, and similar excrescences about the margin of the communication with the sphenoid sinus. The margins of the convolutional impressions in the temporal fossa are markedly elevated, some of them being sharp but most of them rounded and rough. The posterior openings of the optic foramina are considerably narrowed and flattened, especially on the left side, but the anterior openings into the orbits are of normal size.

The mesial portions of the superior orbital fissures are dilated and their lateral margins sharpened. The round and oval foramina are of normal size while the carotid foramina are enlarged in their inner portions and the margins sharpened. The grooves for the middle meningeal arteries on either side are deepened by marginal new bone formation. The posterior fossa shows marked roughening of its entire surface except in the cerebellar fossae. The groove for the right lateral and sigmoid sinuses is large, with exostoses about its margins; the left is small and deep. The

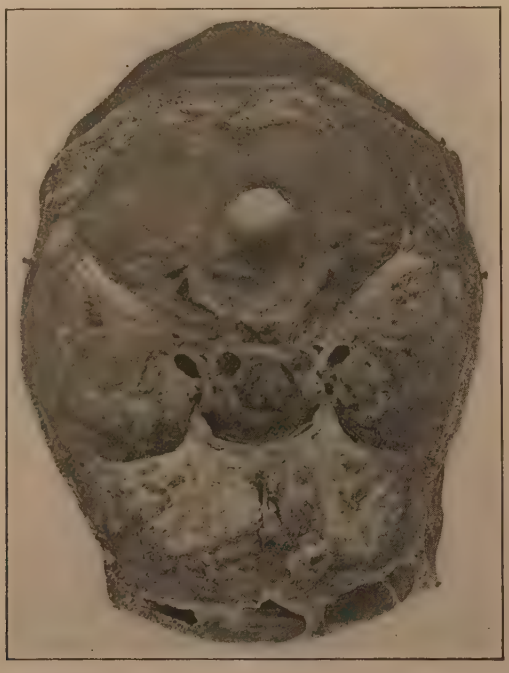


Fig. 9. Floor of cranial cavity showing roughness of bone, large frontal sinuses and sella turcica. (Case of Dean Lewis.)

posterior lacerated foramina are small and on both sides divided by partitions formed from marginal and ligamentous ossification. The clivus is extremely irregular with excrescences at the base of the dorsum sellae. The foramen magnum is irregular and reduced in size. The internal auditory canals are somewhat funnel-shaped from within outward and not reduced in size. The external auditory canals are of about normal size but there is a small warty excrescence on the outer wall of the right canal.

Facial Bones.—The nasal bones are little changed. The orbital openings are somewhat reduced from overgrowth at their superior margins, the remainder of the orbital walls being thin. The lacrymal fossae are deepened and their margins sharpened. The superior maxillary bones are reduced in size, with marked thinning of the bony walls, and deepening of

the infraorbital, canine, and incisor fossae. The antra are greatly reduced in size. The alveolar processes and teeth are approximately normal. The malar bones and zygomatic processes are normal. The palate is markedly deepened, its roof very thin and narrowed in its transverse diameter. The pterygoid processes and palatal bones are thin and delicate. The septum of the nose is thin and markedly deviated to the right. The turbinates are

Fig. 10. Lateral view of skull cap showing thickening of diploë. (Case of Dean Lewis.)

Fig. 11. Base of skull from below, showing unevenness of bone, especially at the foramen magnum. (Case of Dean Lewis.)

relatively thin. The inferior maxilla shows marked progeneum. There is marked elongation of the rami and the angle between ramus and body is widened by 15 or 20 degrees. This has displaced the lower teeth forward for a distance of the width of three teeth. There is moderate bony overgrowth of the margins of the symphysis of the chin, with a grooving of the anterior surface of the symphysis. The thickness of the body and the rami is considerably reduced, especially from grooving along the mesial surfaces. The foramina are of approximately normal size. The condyles, necks, and coronoid processes are normal.

The Spine.—The spine is straight except for slight anterior curvature in the cervical and lumbar regions.[2] There is hyperostosis of the spinous processes, especially in the cervical region, and the tenth, eleventh and twelfth thoracic spines are fused. The supraspinous ligament is ossified at the tenth and eleventh thoracic vertebrae and also elsewhere. All of the thoracic and lumbar interspinous ligaments are ossified. The laminae and articular processes of the tenth, eleventh and twelfth thoracic vertebrae are

Fig. 12. Röntgenogram of head showing huge sella turcica. (Case of Dean Lewis.)

fused. The ligamenta subflava are not ossified below the second lumbar vertebra. The transverse processes also show exostosis and depressions at the seat of ligamentous insertions. The bodies of the cervical vertebrae do not show much change, but from the second to the eighth thoracic vertebrae the bodies show an increase in their anteroposterior diameter and appear slightly wedge-shaped on account of narrowing of their anterior portion. There is ossification of the intervertebral ligament of the entire spine, moderate in the cervical and lumbar regions, extreme in the thoracic re-

[2] This straightness, however, is artificial and produced in the preparation of the skeleton, as the lateral photograph of the patient shows well marked upper dorsal kyphosis.

gion, with complete fusion of the bodies of the tenth and eleventh. The intervertebral foramina are large.

The Ribs.—There is horizontal position of all the fixed ribs,[3] slight downward slope of the floating ribs. Some ossification of the intercostal muscles is seen, also deepening of the subcostal grooves. Ossification is more marked at the lower than at the upper border of the ribs. The first ribs are flat and thin, the second and third moderately thinned. The fifth ribs show a curving downward of the posterior portion, encroaching upon the sixth ribs and also upon the thoracic cavity. The length of the sixth rib with its cartilage is 49 cm. The eighth and tenth ribs show a similar, but less marked, curvature.

Pelvis.—The pelvis as mounted shows an increase in inclination of 25 to 30 degrees. There is almost complete synostosis of the right and partial of the left sacro-iliac joint. The sacrum has large foramina anteriorly but the posterior are small, the left second and third, and the right second being obliterated. There is complete fusion of the bodies of the sacrum, and the first segment of the coccyx is fused with the sacrum. The iliac crests are broadened, especially anteriorly, and show irregular deposits of osteophytes. The wings of the ilia are markedly thin in their middle portions. The surfaces of the iliac fossae are comparatively smooth but the gluteal surfaces have osteophytes at the seat of muscular insertions. The ilio-pectineal lines are sharpened, especially on the left side. The rami of the pubes are reduced in volume on account of marked deepening of the obturator grooves on their under surfaces which reduces the thickness of the rami to one-third of the normal. There is ossification of the obturator membrane at its median insertion to the ischium and pubis with formation of an irregular bony septum, 1 cm. broad, which encroaches on the obturator foramen. The meniscus of the symphysis pubis is narrowed, and there is pronounced lipping of its articular margins. The lateral surfaces of the ischial bodies and rami are markedly grooved, and their superior and inferior margins show marked lipping. This grooving has greatly reduced the thickness of the bones, especially of the rami. The ischial tuberosities are greatly roughened and the spines moderately sharpened. There is marked lipping of the acetabula, including the margins of the cotyloid notches, and so much ossification of the cotyloid ligaments that the cotyloid fossae are almost converted into separate compartments and the cotyloid foramina are enormously increased in size at the expense of the greatly thinned superior ischial rami. The articular surfaces of the acetabula are very irregular, showing evidence of change in the overlying articular cartilages. On the right side the cotyloid ligament is completely ossified at its lower margin. The lipping of the articular margins is more marked on the right side and extends outward into the capsule of the hip joint for 0.5—1 cm. above and 2.5 cm. below.

[3] Largely artificially produced in the mounting of the skeleton.

The Sternum and Clavicles.—The angle between the body and manubrium of the sternum is about 165 degrees (see lateral view of skeleton). The xiphoid appendix is bifid and both prongs are completely ossified and united with the body. There are exostoses at the points of ligamentous insertion in the outer third of both clavicles. Otherwise these bones are normal.

Scapulae.—The scapulae are of about normal proportions but show marked thinning of the bodies and rami, with equally marked lipping of the borders of the bodies and spines, the margins of which are very uneven.

Fig. 13. Röntgenogram of feet. (Case of Dean Lewis.)

The articular surfaces of the glenoid cavities are very uneven, and there is marked lipping of the articular margins and hyperostosis of the margin of the head and neck of the scapula on both sides. The coracoid processes show hyperostosis at the points of ligamentous insertion, but marked thinning of the body of the processes from absorption, especially on the outer side, with production of marked grooving on the lateral surfaces. The acromion processes and spines show similar changes, with thinning of the corpus and hyperostosis at the points of ligamentous insertion.

The Extremities.—The joints of the extremities everywhere show definite evidence of arthritis deformans with erosion and destruction of articular cartilages, lipping of articular margins, and hyperostosis at the points of capsular and ligamentous insertion. (Fig. 13.) All of these changes are especially marked at the articular margins of the shoulders, hips,

elbows and knees. Lipping is fairly well marked in the wrist and ankle joints but destruction of the articular cartilages is comparatively slight. All of the arthritic changes are less marked in the joints of the hands and feet but the ends of the terminal phalanges of both show marked bony overgrowth. (Fig. 14.) There are pea-sized depressions on the plantar surfaces of the proximal ends of the terminal phalanges of the thumbs, and corresponding smaller depressions on the other phalanges, produced by absorption at the base and hyperostosis at the margins of ligamentous insertions.

Fig. 14. Röntgenogram of hand. (Case of Dean Lewis.)

The shafts of the humerus, radius, ulna, and tibia show little change aside from slight sharpening of crests and points of muscular insertion, especially on the upper part of the humerus. The fibulae show marked deepening of the grooves, with reduction in volume and thickening of the crests, making a triangular fluting. The coronoid processes of the ulna are enormously elongated which must have reduced the range of motion at the elbows. The sesamoid bones of the great toes show considerable marginal hypertrophy. The metacarpal and metatarsal bones show a flattening or grooving of the surfaces of the shafts at points of attachment or contact with the interosseous muscles. The phalanges, especially those of the first and second rows, are flattened on their plantar and palmar surfaces from contact with the flexor tendons. There is slight lipping along the sides of these flattened or grooved surfaces.

General Features of Conformation of the Body and of the Skeletal Changes

The appearance of the acromegalic suggests coarseness and brutishness, and at the same time his frequent feebleness and tottering give him an aspect of senility. In fact, both of these features have been commented

upon, especially by authors of anthropological leanings. Thus, Gilford emphasizes the evidences of senilism as well as the simian characters in acromegaly. He states that not only organs and cells but the body as a whole is liable to derangement of growth and development. "There is general weakness, the back becomes bowed, the knees bent, the attitude feeble and the gait tottering so that the acromegalic, like the old man, has to depend upon the help of a stick." He points out that some features of senile decay are of a reversionary nature, and of distinctly simian appearance, and in acromegaly all of these features occur in an exaggerated degree. He applies the general biologic law that late acquired characters are most readily lost; hence the tendency for the reversion of the delicate human hand and foot and the expression-bearing face to a coarser type such as is seen in the anthropoids and in primitive man.

"Some of these simian features of acromegaly are eminently suggestive of a throw-back, if not to an anthropoid, at any rate to a very removed stage of human evolution. The heavy, beetling eyebrows which give such a sinister cast to the countenance of some old men are very distinctly a relic of an older and more brutish stage of evolution." He adds that the primitive paleolithic man must have had a strikingly acromegalic appearance on account of his prominent supraorbital ridges, large nose, heavy jaws, and tall, thick-set, clumsy figure.

Another Englishman who discusses acromegaly from the anthropologist's viewpoint is Arthur Keith. He calls attention to the similarity of the typical acromegalic skull to that of the Neanderthal man, the most ancient type of European yet discovered.

"In both types the skulls are particularly long and low, the eyebrow ridges are prominent; the muscular markings are pronounced; in both, the facial parts of the skull are long and wide." In 1863 T. Huxley called attention to the characteristics of the Neanderthal skull and Barnard Davis then produced an acromegalic skull as proof that a similar formation could be found among modern men. In 1872 W. A. Freund of Berlin described a case of acromegaly under the name of "macrosomia partialis" and called attention to the resemblance of the skull to that of the gorilla and chimpanzee. D. J. Cunningham in 1878 was the first Englishman to describe fully a case of acromegaly and also the first to call attention to the relationship between what is now known as acromegaly and gigantism. He, too, commented on the anthropoid nature of the cranial characters. These early authors who were under the influence of Darwin looked upon acromegaly as an instance of atavism, a theory which was discarded as obsolete when the dependence of acromegaly upon hypophyseal disease was demonstrated.

Keith assumes that the anterior lobe of the hypophysis produces a hormone which "renders the osteoblasts hypersensitive to the various stresses which fall on the human skeleton during life. Thus, the osteoblasts at the

origins and insertions of muscles become increasingly sensitive to the traction of the muscle fibers; the muscular impressions and processes of the skeleton become unduly raised, extended and emphasized by the formation of new bony matter. The parts and articular surfaces of bones exposed to repeated pressure or tension become the seats of growth."

Keith wishes to call particular attention to the following two points:

1. That the changes in acromegaly are of the nature of true growth and are apparently due to the circulation through the body of a substance formed in the pituitary. This substance seems only to sensitize the tissues, the actual cause of this growth being mechanical stimuli arising from muscular action and mechanical movement.

2. The growth changes seen in the acromegalic are of the same nature as those which occur normally in anthropoids and the Neanderthal race and both are probably due to a condition of hyperpituitarism.

Sternberg, in his monograph, makes the following general statements regarding the bone changes: "The disease is generally symmetrical, but of a pair of bones, one may be more markedly affected than the other. The deepening of the canals for the vessels, dilatation of the vessel foramina, and strengthening of the points of attachment for the muscles and ligaments are typical. As a result of this, the bones acquire a coarse appearance, and the normal roughness of the surface is thereby increased. This change of shape exhibits a partial exaggeration of the normal proportions. Moreover, small exostoses appear on the outside of the muscular and ligamentous attachments. Minute consideration of the normal topographical relations is often necessary regarding these osseous deposits to distinguish them from the former. They are small, rarely prickly, and are placed most abundantly on the bones of the base of the skull, vertebrae, pelvis, and chest, very few on the bones of the extremities. They are far more scanty than the normal strong points and prominences. Prickly, warty, stalactiform exostoses are never found to any great extent in true massive acromegaly on normally smooth parts of the bones. Typical, further, is a peculiar growth of some bones (lower jaw, bones of the air sinuses, sternum). The tumor of the pituitary body produces in most cases special changes in the sphenoid bone. The extent of the changes depends naturally on whether, on dissection, the case is found to have reached an early or later stage."

More recently, Biedl, in his book on Internal Secretion thus characterizes the skeletal condition: "The changes in the bones are not as pronounced as the clinical symptoms would seem to show. The ends of the bones and the terminal phalanges are undoubtedly broadened and enlarged, but this is chiefly due to exostoses and irregular absorption of the cortical layers, and to bony outgrowths at the joints—changes which must be regarded as secondary results of the hyperplasia of the soft parts. The clavicle is usually very much enlarged. In addition to the changes in the

sphenoid bone, the bony skull shows premature obliteration of the sutures; exostoses, especially of the muscle attachments; enlargement of the antrum and of the frontal sinus; increase in the volume of the superciliary arch, the zygomatic arch, and the inferior maxilla. Investigation of the histology of the bones shows that the changes usually are due, not to specific pathological processes, but to the deposition and resorption of bony substance, in a manner identical with that of the normal growth of bones. In addition, hypoplasia or degeneration of the sexual glands is a frequent accompaniment of the condition."

Fig. 15. Spine shows co-ossification of bodies of dorsal vertebrae and many bony unions of spinous and transverse processes. (After Osborne, Yale Med. Jour., Dec., 1897.)

There is agreement among most authors on the point that the bone changes essentially represent a reaction and readjustment secondary to the enlargement of the soft parts, hence the emphasis on thickening at points of muscular and ligamentous insertions. The fact must not be lost sight of that rarefaction and absorption of bone is as characteristic a feature as the progressive changes. The regressive changes are particularly emphasized by H. Curschmann. The finer changes in the bones, which are said to consist of thickening of the osteogenic layer of the periosteum and increase in the spongy at the expense of the compact substance, were early studied in detail by Duchesneau and are thoroughly discussed in the excellent review of M. B. Schmidt(*a*). Osborne, one of the first Americans to describe an acromegalic skeleton, called attention to the fact that all of the spongy bones of the body are more or less thickened, and that all articular surfaces, whether of long or spongy bones, show a tendency to spread out, widen and grow more prominent. The flat, thin bones, while increasing in

extent show a tendency to become thinner in their plates. Osborne also comments on the enlargement of all crests, tuberosities and eminences in the direction of muscular action and finds this due to part of the tendons becoming coössified with the bones rather than to a reaching out of the periosteal bone formation. On the whole, the description by Osborne is very similar to that given of the skeleton of our own case. (Figs. 7, 15.) He, too, found osteophytes in the joints and roughened articular surfaces. Furnivall also described bone deposits at the attachment of muscles and ligaments and at the margins or articulations, but in his case the joints themselves were not affected. The joints were also normal in Israel's case.

The Skull.—We will not enter into details regarding other bones, but the changes in the skull, on which depend the earliest and most reliable diagnostic signs of the disease, deserve especial mention. They have been analyzed in a most lucid and original manner by Keith.

Availing himself of all the acromegalic skeletons to be found in London, Keith attempted "an exact inquiry into the nature of the growth changes of the skeleton, particularly of the skull."

Growth Changes in the Palate.—"By the palatal area is meant the space bounded anteriorly and at the sides by the outer alveolar margin and behind by a base line drawn from one side of the palate to the other behind the last molar tooth. This area is actually diminished in the acromegalic, especially that of the lower dental arcade." "Besides the reduction in the size of the lower alveolar area there are also certain constant and well marked growth changes in the alveolar part of the lower jaw of the acromegalic:

"1. The width between the last lower molars is increased in the mean by nearly ten mm. so that the right and left lower molars, in place of being nearer together than the upper are wider apart and project beyond the upper dental arcade.

"2. The canines are advanced so as to come more nearly into a transverse line with the incisors.

"3. Porous vascular bone is heaped upon the alveolar margin elevating the dental sockets. The vault of the hard palate is thus increased; the mean height of the alveolar margin measured from the hard palate opposite the second molar tooth is 17.5 mm. in the acromegalic and 12.5 in English students. Similarly, the lower alveolar margin of the mandible is raised, the tooth sockets being elevated at the same time. The separation of the teeth which occurs in acromegaly is due to the alveolar or socket elevation, not to a linear increase of the alveolar margin. The growth at the alveolar margins and the elevation of the dental sockets are supposed to be stimulated by the pressure brought to bear on those parts during mastication. Pressure cannot influence the linear dimensions of the alveolar arch; that depends on the number and size of the teeth."

Growth Changes in the Mandible.—"As regards the body of the jaw,

growth is seen to have taken place (1) in the alveolar margin, (2) on the mental eminence, (3) on the lower margin anterior to the groove for the facial artery. The most remarkable changes are seen in the ramus; the double process of deposition and absorption has completely altered the character of the ramus. (Fig. 16.) It has become markedly narrower; the region of the angle has been absorbed and hence the appearance of an opening-out of the angle between the ramus and the body of the jaw in the acromegalic. The ascending ramus has increased in height. Its average height in the normal as measured from the lowest insertion of the masseter to the upper surface of the condyle is 65 mm. while in three acromegalic

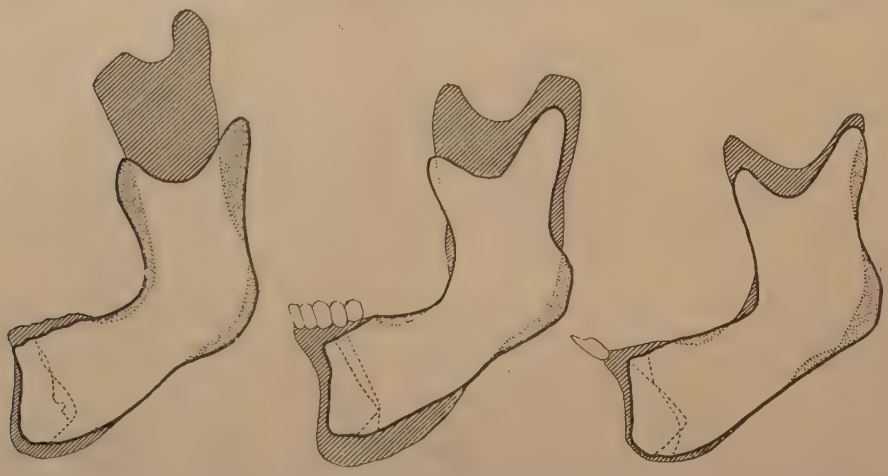


Fig. 16. Drawings of lower jaw from cases of acromegaly contrasted with drawings from normal English skull (indicated by heavy outline). The dotted areas are those which are absorbed, the shaded those which are deposited. (After Arthur Keith, Lancet, Lond., 1911.)

skulls it measured 90, 92, and 95 mm. respectively. The growth has taken place at the points of pressure (temporo-maxillary joint) and traction (coronoid process)." Another growth change is caused by absorption of bone from the inner side of the ramus and deposition of bone on its outer side so that the rami become more widely separated which increases the width of the mouth and pharynx.

Keith similarly compares the bone changes in the temporal, frontal and occipital region of the skull of acromegalics with normal and gorilla skulls. Thus he points out that the forward growth of the frontal bone leads to a most remarkable transformation. "When viewed in absolute profile the anterior part of the temporal ridge falls 15 to 20 mm. behind the line of the frontal pole of the brain in normal crania but in acromegaly this ridge may pass forward until it is in a line with the frontal pole or it may even pass in front of it. We have here a key to the great growth of the supraorbital ridges and expansion of the frontal sinuses in the acro-

megalic. The external angular process of the frontal bone and ascending process of the malar—the whole outer wall of the orbit—is actually prolonged or moved forward. Not only so, but the zygoma in relation to the cranial cavity is lowered, thus increasing the height of the temporal fossa by depressing its floor. The external auditory meatus in some cases is depressed 10 mm. or more." The temporal development causes a forward growth of the orbital region. The external angular process of the frontal bone and the ascending process of the malar occupy a position from 10 to 15 mm. further forward and downward than in the normal skull. The nose becomes long and remarkably prominent but the nasal bones are very little enlarged. The great development of the supraorbital region of the forehead has forced the root of the nose downward and forward. *In the orbit* the chief change concerns its outer wall, the enlargement of which is connected with that of the temporal bone. The growth of the malar bones and zygoma is striking and apparently stimulated by the traction of the masseter.

Vault Changes.—The changes in the vault of the skull are most marked in the frontal region. Thus, between the origin of the temporal muscles a strong sagittal arch of bone is built up so as to provide a strong fulcrum for these muscles and the same condition is present in the gorilla.

Occiput.—In the occipital region a wide crest may form in the region of the superior curved lines corresponding to a similar formation in the anthropoid apes. The area of insertion of the muscles of the neck is greatly enlarged, the inion is moved upward and the mastoid processes are wider apart by 10 to 25 mm.

Sella Turcica.—The sella turcica is of particular importance as röntgenologic demonstration of its enlargement constitutes one of the earliest indications of hypophyseal tumor. The honor of having pointed this out as early as 1899 belongs to Oppenheim(*a*). It has been most minutely investigated in the living and in dead subjects, and numerous authors supply us with illustrations of innumerable normal and abnormal variations in its size and shape, as well as with detailed measurements. Keith gives the following dimensions in normal male skulls: antero-posterior diameter 10 to 12 mm., transverse diameter 14 to 15 mm., depth 8 mm. Cushing states that profile radiographic measurements exceeding 15 mm. anteroposteriorly and 10 mm. in depth may be looked upon as indicating an enlargement. Howe gives the measurements by different authors, pictures tracings of the sellar outlines of forty normal individuals and rightly concludes that "the pituitary fossa is normally subject to great variations in size and outline and gives no information concerning the condition of the pituitary gland unless there is very marked sellar enlargement or absorption of some portion of the bony envelope." Schüller(*a*) has shown that the two commonest variations—the short and deep and long and rather flat types of sella—seem to depend on the general shape of the skull, whether

brachy—or dolichocephalic. Gibson, Fitzgerald, Fearnsides and Peritz contribute further data on the normal and abnormal sellae. According to Cushing there are three principal types of the pathologically deformed and enlarged sellae: (1) that associated with thickening of the clinoid processes and dorsum ephippii; (2) that with thinning from pressure absorption of these parts, and (3) that with more or less destruction of all outlines. The first type, he says, is confined to the cases of acromegaly and gigantism which are uncomplicated by adenomatous struma formation, and the thickening is explained by the general tendency toward osseous overgrowth.

The Skin and Its Appendages

The skin is usually rough, thickened and thrown into folds. The condition in some respects resembles myxedema, and, as pointed out by Strümpell, is the opposite of scleroderma. The puffiness of the skin is most marked in the palms and soles. The cutis vera is thickened, and hypertrophy of the papillae is marked so as to cause them to project like small polypi. The epidermis is rather thin on account of its being stretched over the papillae (Dalton). Unlike the skin of myxedema, that of acromegaly in spite of its sclerotic condition may be raised into folds. In rare instances the scalp is thrown into large folds resembling cerebral gyri, hence the term *"cutis verticis gyrata,"* described in acromegaly by Sabat and by Adrian and ascribed to the more rapid growth of the skin than of the bone.

Pigmentation of the skin occasionally may be marked, and its resemblance to that of Addison's disease suggests associated adrenal changes (Climenko and Strauss; Bendell). Acanthosis nigricans in both axillae is described by Fâhræus and attributed to the adrenals.

Mollusca fibrosa are frequent and sometimes sufficiently abundant to constitute von Recklinghausen's disease. Combinations with the latter disease are reported by Wolfsohn and Marcuse and by Nicolas and Favre.

More or less hypertrichosis is the rule and it is usually pronounced in cases of marked cutaneous pigmentation. One of Cushing's male patients (case XXV in his monograph) had excessive growth of hair all over his trunk and arms, marked brownish pigmentation in the groins and about the navel, general asthenia and low blood pressure. Falta(*b*) has made similar observations. Ausch observed the previously blond and soft hair of an acromegalic and diabetic man of 38 years turn black and coarse. The hairy growth was not excessive except on the face and lower abdomen. A polyglandular affection existed since necropsy revealed enlarged thymus, thyroid and adrenals, with histologic changes in the latter. The nails may be striated and appear too small for the enlarged fingers.

Both sebaceous and sweat secretion are prone to be increased. Brooks

found a "surprisingly large number of sweat glands of large size" in sections of the skin. Falta points out that hyperidrosis occurs independently of increased thyroid activity and must be a feature of acromegaly as such. According to Hinsdale the electric conductivity of the skin is increased, as is the case in Graves' disease, the decreased resistance ("Vigouroux's sign") being attributed to dilated cutaneous blood vessels.

The Muscular System

Muscular weakness is a notable feature except in the early stage and is attributable to the endocrin disorder rather than to any primary muscular affection. Extensive muscular atrophy is rare though in a case reported by Duchesneau it was sufficiently marked to lead him to assume the existence of an "acromegalic myopathy," but this has not been borne out by further experience. Equally rare are signs of true myasthenia, the only observations of myasthenic reaction being those of Franchini and Giglioli who maintain that the asthenia in acromegaly reaches a degree only equaled in true myasthenia gravis and Addison's disease. Those who have made histologic examination of the muscles generally dwell on the degenerative, atrophic and sclerotic changes. Martinotti believes this stage is preceded by one of hypertrophy as he observed an increased diameter of the muscle fibers and proliferation of the sarcolemma nuclei. Brooks also observed mitoses in these nuclei. The supposition that a preliminary stage of muscular hypertrophy exists is greatly strengthened by the fact of the characteristic bony hypertrophy at points of muscular insertion which we have described as being the most striking skeletal change.

The Upper Respiratory Tract

Enlargement of the nose, especially in width, is a regular feature and involves bones, cartilages, and soft parts. The larynx also shares in the hypertrophy. The voice grows deeper, harsh, or guttural, a condition which is ascribed largely to changes in the larynx, and partly to the enlargement of the accessory sinuses (Marie). The acromegalic larynx has been the subject of special studies. Chappell described a patient who died during an attack of dyspnea. The epiglottis was thickened, the arytenoid cartilages and the ventricular bands were enlarged and the glottic aperture was very small. Chevalier Jackson gives a detailed description of the laryngoscopic appearances in four patients, one of whom required tracheotomy for laryngeal stenosis and some time later died suddenly, apparently of asphyxia. "External palpation of the larynx revealed it to be of enormous size, the enlargement seeming even and symmetrical. (Fig. 17.) Laryngoscopic examination showed a general overgrowth of the larynx.

The epiglottis, aryepiglottic folds, ventricular bands and vocal cords were proportionately enlarged. An appearance of asymmetry was given by the deviation of the long axis of the glottis, which, instead of being sagittal, was deviated to the left, posteriorly. The glottic chink was very narrow and was insufficient for breathing. The left aryepiglottic fold was as much

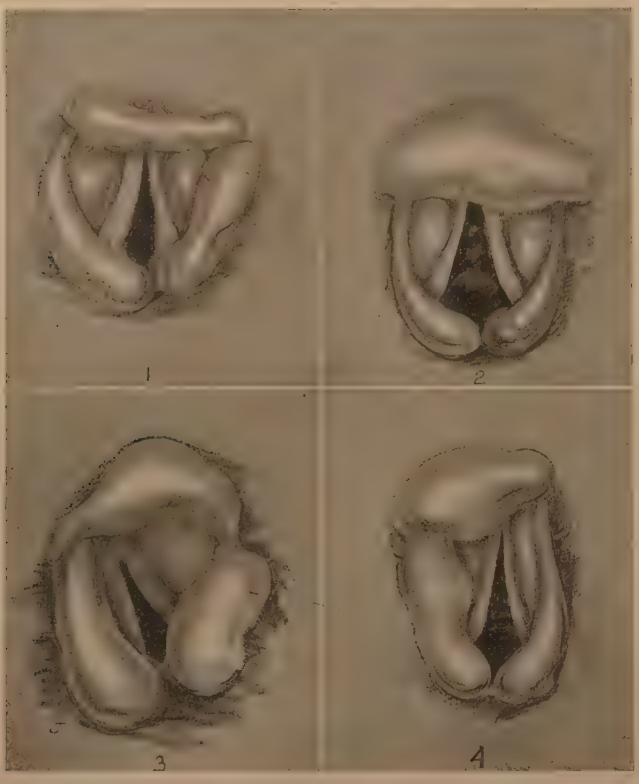


Fig. 17. The Larynx in Acromegaly. (After Chevalier Jackson, J. Am. M. Assn., 1918.)

thickened as the right, but was not so long. The whole laryngeal image was strongly suggestive of the facies and 'ginger-bread hands' of acromegaly." The changes in the other cases were similar. Beck briefly describes apparent redundancy of the laryngeal mucous membrane.

The Circulatory System

Hypertrophy of the heart is usually met with, and is combined with a general visceral enlargement (splanchnomegaly). There is also a general dilatation of the blood vessels with sclerotic changes, and further causes for vascular thickening and cardiac hypertrophy are found in the fre-

quently observed adrenal hyperplasia and in the presence of pressor substances in the blood (Humphrey and Dixon; Amsler). There is a tendency to increase in blood pressure (Peritz). Some of the earlier authors (Klebs, Brooks) lay great emphasis on the changes in the blood vessels which they maintain are among the earliest observed. According to J. B. C. Fournier two varieties of enlarged heart are met with: one due to simple cardiomegaly with normal muscle and very rarely associated with valvular insufficiency; the other with veritable interstitial myocarditis and accompanied by signs of arteriosclerosis and impaired heart's action, passive congestion of the liver, edema of the extremities, etc. This author also believes that the deformities of the spine may lead to dilatation of the right side of the heart.

Varicose veins and hemorrhoids are common. Signs of Raynaud's disease, such as blueness and coldness of the hands, have been observed (Boettiger, Oeconomakis) but in some of the reported cases the presence of acromegaly was not proven.

Paroxysmal hemoglobinuria and joint swellings of the nature of intermittent hydrops were noted by Chvostek. Dunn observed attacks of hemoptysis ascribed to transient hemorrhagic edema of the lungs.

Metabolic Disturbances

Glycosuria.—In 176 cases of acromegaly collected from the literature up to 1908, L. Borchardt found 63 complicated with diabetes, and in eight other cases with alimentary glycosuria, so that in 71 cases, or 40.32 per cent, an abnormal carbohydrate metabolism was demonstrable. In some cases sugar appeared in the urine only occasionally and, in general, the glycosuria is remarkably independent of the diet. He believes that the glycosuria is caused by hyperfunction of the hypophysis as he succeeded in producing glycosuria in rabbits by subcutaneous injection of pituitary extract. By a series of control experiments he convinced himself that the glycosuria was not produced by admixture of epinephrin.[4] Cushing's experiments gave similar results, and he also found that administration of posterior lobe extract lowered the sugar tolerance to normal or below normal in animals in which it had been raised by excision of the posterior lobe. He associates glycosuria especially with the early and active stages of acromegaly. His finding of glycosuria in a case of hemorrhage into the posterior lobe of the hypophysis after skull fracture is also very suggestive. Labbé points out that when acromegaly and diabetes coexist the former appears first, and that polyuria is likely to persist after the sugar

[4] On a priori grounds the participation of epinephrin in such phenomena is highly unlikely. It would involve complete inhibition of gastro-intestinal peristalsis.—R. G. H.

has disappeared. He is convinced that the theory of associated pancreas lesions (Forschbach and Severin) in diabetic acromegalics does not hold and believes that sugar regulation is controlled by a complicated physiologic mechanism in which liver, pancreas, nervous system and glands of internal secretion participate and a lesion of any one of these parts suffices to produce glycosuria. It is of scientific interest that Levy and Boulud's production of glycosuria in dogs by intravenous injection of the cerebrospinal fluid of an acromegalic patient supports Cushing's view that posterior lobe secretion passes into this fluid.[5] Anders and Jameson collected 183 cases of hypophyseal disease with mention of the condition of the urine, reported during the five years following Borchardt's report, 1909-1913 inclusive. Glycosuria was present in 28 cases and 16 of these were instances of acromegaly. There were 88 cases of acromegaly in the series, hence 18.2 per cent with glycosuria.

Other Metabolic Disturbances.—In a general way, the metabolic studies so far reported have not yielded uniform results, and are difficult to evaluate clinically as too little attention has been paid to the stage of the disease at the time of study. Retention of calcium,[6] nitrogen, phosphorus and magnesium was noted by Moraczewski; of calcium, nitrogen, and phosphorus by Edsall and Miller; of calcium and magnesium by Franchini and Giglioli; of calcium, magnesium and phosphorus by Bergeim, Stewart and Hawk. Falta and Nowaczynski in three cases found the elimination of endogenous uric acid twice or more than twice that of normal persons. H. Salomon found the basal metabolism increased in two robust male patients, not increased in two women while Means found it lowered in his case and ascribed this to the great weight of the enlarged bony structures, bone, like fat, being an inert tissue and reducing the calories per kilogram.

The blood is often found at necropsy to be increased in quantity. Both polycythemia and slight anemia may occur. Relative lymphocytosis is common (Falta; Steiger), as is slight eosinophilia (Cushing; Steiger). Rarely normoblasts and myelocytes, attributable to alterations in the bone marrow, are found (Franchini and Giglioli).

The Genital System

As has previously been pointed out there is in acromegaly an early tendency to an exaggeration of the male secondary sexual characters, and for those of the female to assume a male type, namely: increased and more diffuse growth of hair, involution of the breasts, and change of the pelvic

[5] Jacobson has recently restudied the problem and has reached the conclusion that such secretion does not occur. Johns Hopk. Hosp. Bull., 1920, xxxi, 185.—R. G. H.

[6] According to Blair Bell calcium retention is a masculine characteristic; hence this feature is another example of the frequently emphasized tendency to exaggeration of the male sexual characteristics.

bones to a male type. The penis, and particularly the clitoris, may participate in the general enlargement of end segments ("acra").

Sexual desire and power remain intact or may be increased during the early stages in most cases, but almost invariably a subsequent rapid decline takes place, hence in the fully developed disease impotency in the male and amenorrhea and sterility in the female are the rule. Blair Bell ascribes the amenorrhea to the above mentioned tendency to masculinity. Falta knows of only two instances of conception during acromegaly, one of his own cases and that of Pirie. This latter patient was a woman of 43 years who conceived three months after the onset of amenorrhea and other acromegalic symptoms. She developed a beard, the hair on her head "stood straight upwards," there was yellow bronzing of the skin of the face, chest and inside of the thighs. The vagina and clitoris were large. Several other cases may be added, e. g., that of Kalleday in which a normal pregnancy followed three months of ovarian treatment, and that of Tibor in which at least two out of ten pregnancies occurred after the onset, and menstruation persisted for ten years after the onset. Boyd looked up the sexual data in 65 reported cases and found loss or decided impairment of sexual function in 68 per cent of the males and 89 per cent of the females. With declining function involution of the testicles, ovaries and uterus takes place so at necropsy these organs usually are found to be decidedly atrophic.

The discrepancy between the behavior of the secondary sexual characters and genital function is now readily understood, thanks to Steinach's important demonstration that the former depend entirely on the interstitial cells of Leydig so we merely have to assume a preliminary stimulation or hyperplasia of these structures which process may be connected with and at least is followed by decreased activity of the tubular sexual glandular structures.

Milk secretion sometimes appears from activation of the mammary glands. Bab reports the case of a woman of 35 years whose menstruation ceased from January, 1903, to May, 1904. In the spring of 1903 she received a psychic trauma by lightning striking near her, and then developed the usual signs of acromegaly. Colostrum appeared and also a growth of hair on the chest. Roth observed milk secretion in a man of 28 years, and the nature of the secretion was confirmed by chemical and microscopic examination. Fazio observed galactorrhea lasting for four years.

Associated Endocrine Disturbances

Throughout this narrative the interweaving of symptoms attributable to endocrine glands other than the hypophysis has been pointed out. Here we shall merely summarize certain data.

Thyroid.—This gland is usually diseased. Furnivall found it normal in only five of 29 cases. The pathologic changes, however, are very variable. While hypertrophy is common, combination with actual Graves' disease is rare. It did not exist in any of Cushing's numerous cases but has been reported by a few others (Murray; Lancereaux(*b*); Anders and Jameson). Myxedema received early mention by Ponfick(*b*), and the relation of the two conditions is thoroughly discussed by Millioni who observed both fully developed in one patient. Such a case is also described by Greene.

Parathyroids.—No account of lesions of these organs or of signs of tetany have been met with.

Thymus.—Dullness over the manubrium sterni is not a reliable sign of enlargement of this organ on account of the bony thickening. However, persistent thymus has frequently been found post mortem (Cushing, case II, Claude and Baudouin, Eltester and Schroeder, Ausch and others). In Yamada's clinically typical case the thymus was greatly enlarged and there was a marked status lymphaticus but the hypophysis is said to have been perfectly normal.

Adrenals.—Pigmentation of the skin, asthenia and low blood pressure suggest adrenal insufficiency, and in a few cases high blood pressure has been attributed to adrenal overactivity (Cushing). The adrenals have often been found enlarged at necropsy (Amsler, Ausch, Eltester and Schroeder, Mullaly(*a*), Harbitz, etc.).

Pancreas.—Its possible, but contested, relation to the frequent glycosuria is discussed elsewhere. It has frequently been found enlarged in connection with general splanchnomegaly, hence the importance of the enlargement of a particular organ is less obvious.

Pineal Body.—Few observations are available. Bartlett found it enlarged to twice its normal size in a case of acromegaly with polyglandular involvement. Schultze and Fischer report a similar case. Sexual hyperactivity preceded the impotence in this case which is of interest in connection with the sexual precocity observed in children with pineal tumor (see chapter on Gigantism).

Psychoses

We have already discussed the tendency to apathy, lassitude, drowsiness and mild depression present in very many cases. The first case report of a true psychosis in connection with acromegaly is probably that of Arnold Pick (1890), as Souza-Leite, in his thesis of the same year, stated that, while there is a tendency to depression to the point of suicidal desire, actual insanity had not been observed. These milder mental changes were noted in 10 of his 38 collected cases, and in four of Duchesneau's 14 additional cases (1891). A good example of a borderline state is related by

Thomas K. Davis as occurring in a case of arrested acromegaly in a man of 28 years. After the disease had reached a disfiguring stage he became unable to meet either strangers or old friends. "He has several times broken down and cried in public places because there his thick lips and unshapen jaw, he feels certain, are the cause of unfriendly comment. He shows deep emotion when telling any one of his trouble. He can initiate no plans because his mind is lost in thinking of his affliction; he has no longer the ambition or the confidence natural to him."

Pick's patient, a man of 47 years, whose brother was insane, had two attacks, seven years apart, diagnosed "acute hallucinatory paranoia" from which he recovered. With our present conceptions we would suspect that the case was one of manic-depressive insanity on hereditary basis and that there was no relationship between the psychosis and the acromegaly. In a thesis on the mental state of acromegalics published in 1899 Brunet collected six cases of insanity, namely, that of Pick, one of his own and others reported by Tamburini, Thomas, Joffroy, Garnier and Santenoise. If he had perused the American literature he would have found more. In 1891 Berkley reported a case in an insane colored woman, 60 years old, also claimed to be the first case of acromegaly observed in a negro. Hutchings, in the annual report of the St. Lawrence State Hospital for 1894, described a case of "mental enfeeblement in acromegaly" which he reported more fully, and with necropsy, in 1898. The subject had been arrested as a tramp in 1885 and was afflicted with a dementia which gradually increased until his death in 1894. A tumor of the hypophysis was present. Hutchings also relates a second case in a man of 44 years, weak minded from birth, and epileptic from the age of seventeen. This author commented on the fact that both of these patients were intolerant of tight bands in the clothing which one of them said gave him a feeling of suffocation and burning in the chest. This sensation and the delusion of being suffocated by gas existed in an insane acromegalic woman observed in an English asylum by David Blair. Worcester reported, with necropsy, a case in a demented female inmate of Danvers (Mass.) State Hospital who also had presented features of myxedema which cleared up on thyroid treatment.

Profound deterioration must have existed in the necropsied case of Eltester and Schroeder, since the patient was described as demented and apathetic, unable to feed himself or to speak any distinct words. In addition to hypophyseal tumor, the thymus, adrenals, and pancreas were enlarged. In one of the cases reported by Harbitz, also with hypophyseal adenoma and adrenal changes, dementia must also have been extreme, as the patient, a woman, 28 years old at death, "became like an animal and died an idiot." Such profound dementias occur with any kind of organic brain disease, including tumor in various localities, and cannot be considered connected directly with the acromegalic condition. Alfred Gordon,

in discussing the mental symptoms in cases of intracranial tumor, states that neither the location nor the nature of the tumor can be inferred from them.

The manic-depressive type of psychosis is the one by far most frequently observed in acromegaly, as has been well shown by recent investigators, notably Laignel-Lavastine, and Parhon and Stocker. The former author believes thyroid disturbance plays a rôle in the production of the psychoses. Léri (1908) makes a similar claim for the adrenals, and both of these contentions are supported by numerous reports of changes in these organs in cases complicated by psychosis, several of which have been mentioned here. The case of Garnier and Santenoise previously mentioned was called "acute mania" and was complicated by goiter. J. Salomon observed an acromegalic man with three depressive attacks which were aggravated by administration of hypophysis and improved by thyroid. Parhon and Stocker's patient had two cycles of the manic-depressive psychosis which these authors connect with the endocrin disturbance, supporting themselves also on the rather numerous reports of the same psychosis complicating Graves' disease (Gelma).

A chronic paranoid state with hallucinations was evolved in Meyer's patient and in that of Goldstein(*b*) who developed acromegaly after removal of the ovaries. Witte pictures and describes an old man who developed acromegaly at 55 and finally was bedridden with numerous somatic symptoms for a long time preceding his death at 69. This man had fleeting hallucinations and delusions which the author explains thus: The patient who had a psychopathic inheritance and small mental endowment could not resist the abnormal stimuli arising from the altered portions of the body and gave them a delusional interpretation. Like other patients with optic atrophy he had subjective visual perceptions, saw men with knives, and soldiers; olfactory nerve irritation caused him to imagine he smelled burning human flesh with the resulting delusion that he was to be burned; tactile paresthesias in the hands made him think he was holding his wife's hand; painful sensations, that wire was being wrapped around him; altered pressure sense, that iron bars had been put inside his limbs, etc. Witte adds that this type of psychosis is uncommon in acromegaly in comparison with depressive and simple deteriorated states.

To sum up: Mild psychoneurotic symptoms, such as apathy, feeling of inaptitude for work and moodiness occur in a very large number of cases of acromegaly after the disease has become well established. A further evolution into psychoses of the manic-depressive type, with preponderance of the depressive phase, takes place in a limited number of cases. Rather than ascribe them to hypothetical hypophyseal, thyroid and adrenal influences, or to worry over disfigurement of the features, we remain on safer ground if we connect these psychic ills with the precocious sexual involution which is known to be a feature of acromegaly in both sexes. It is significant that the prevailing climacteric psychoses are very similar in

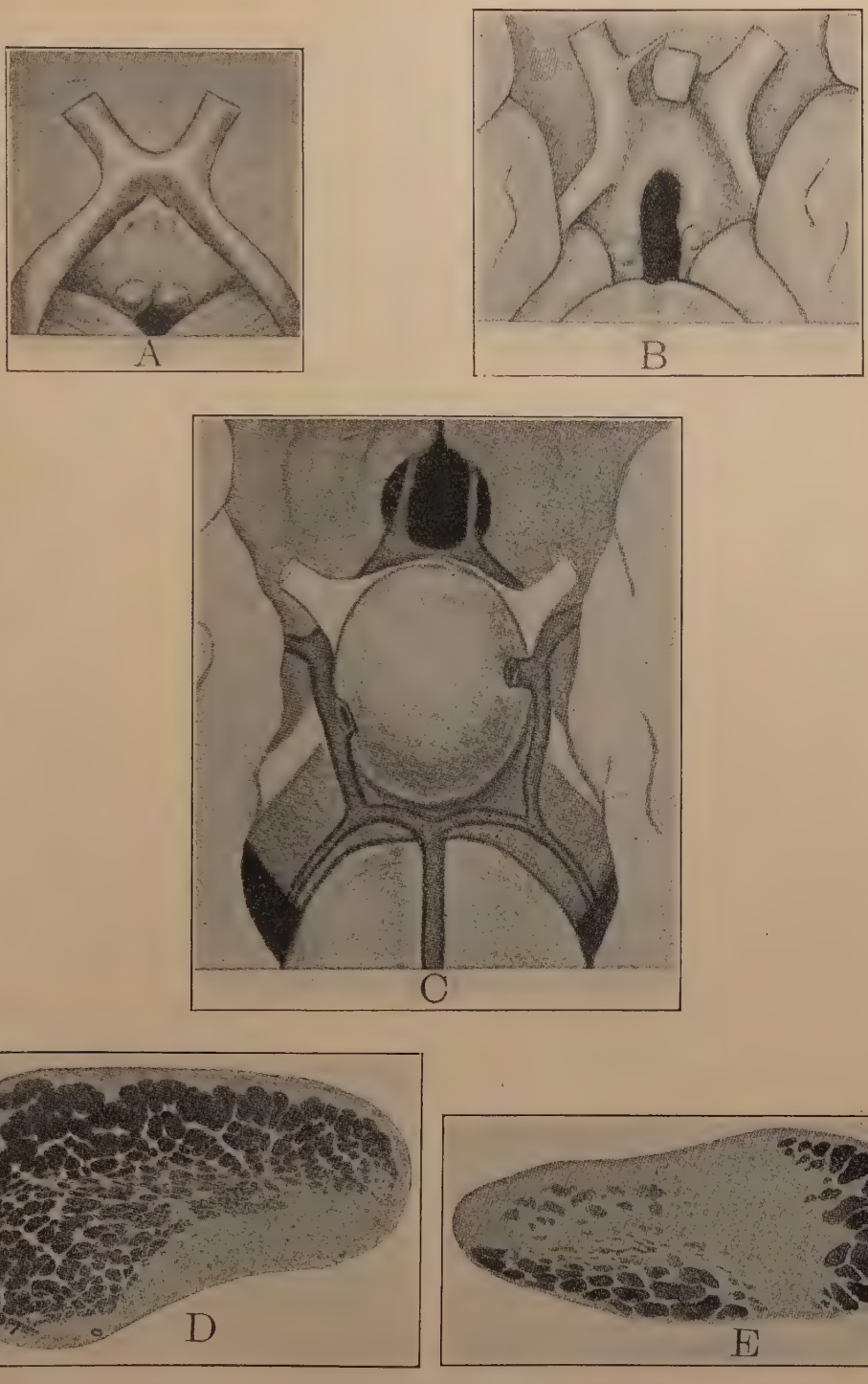


Fig. 18. Changes in chiasma and optic nerves. A. Chiasma in Case 1 after removal of hypophysis. B. Chiasma in Case 3 after removal of hypophysis. C. Chiasma and tumor in situ in Case 2. D. Right optic nerve. E. Left optic nerve. (After W. A. Holden, Arch. Neur. & Psychopathol., 1899.)

kind. We are glad to note that Peritz(*a*) takes a similar view. In some cases the psychosis clearly is dependent on compression or direct invasion of the brain by tumor, or on hydrocephalus, as is frequently seen in tumor of any portion of the brain.

Secondary Symptoms and Lesions

Ocular Symptoms.—These are practically always produced mechanically by the pressure of the hypophyseal tumor on the chiasma, nerves and tracts and by deformity of the orbits. Thus Dr. Mark's chief ocular disturbance was caused by constant change in the character of his astigmatism ascribed to pressure on the eyeball by hyperostosis of the orbits. Oppenheim(*b*) (1914) makes the interesting suggestion that in exceptional instances optic nerve degeneration, analogous to the rarely observed spinal cord degeneration, may be produced by a toxic substance furnished by the hypophysis. With this possible exception the explanation for the eye symptoms must be found in the complicated mechanical conditions created by a growing hypophysis and a changing sella in the immediate vicinity of the optic chiasma. (Fig. 18.) As a result of the sellar widening the optic foramina become farther separated, necessitating additional readjustment. The usual sequence of events was stated by Holden in 1899: "First, the posterior portion of the chiasma is compressed by the pituitary body. Following this, the posterior and middle portions of the chiasma are flattened and forced upward, and thus separated from the anterior portion which is protected by the bone beneath it. (Fig. 19.) Later, with this tilting upward of the chiasma posteriorly and the forcing forward of the anterior wall of the pituitary fossa, the anterior portion of the chiasma is encroached upon by the pituitary body and arched directly forward. Finally the chiasma may be severed completely." With the pressure mainly exerted on the chiasma the decussating fibers going to the nasal sides of the retina suffer most, and consequently bitemporal hemianopsia constitutes the commonest visual defect. The types of field encountered have been worked out most carefully, among others by Arnold Josefson, Cushing and Walker, and de Schweinitz.

Optic atrophy and its resulting visual impairment are said to be much less frequent in acromegaly than in other forms of hypophyseal disease. Uhthoff(*a*) found amblyopia and amaurosis in 7 per cent of the acromegaly cases and in 28.5 per cent of cases of other hypophyseal affections.

De Schweinitz classified the eye symptoms as follows:

1. Impairment of vision, varying from blurred sight to amaurosis or complete blindness.
2. Intraocular optic nerve alterations varying from partial or general pallor of the nerve head to partial or complete atrophy; less

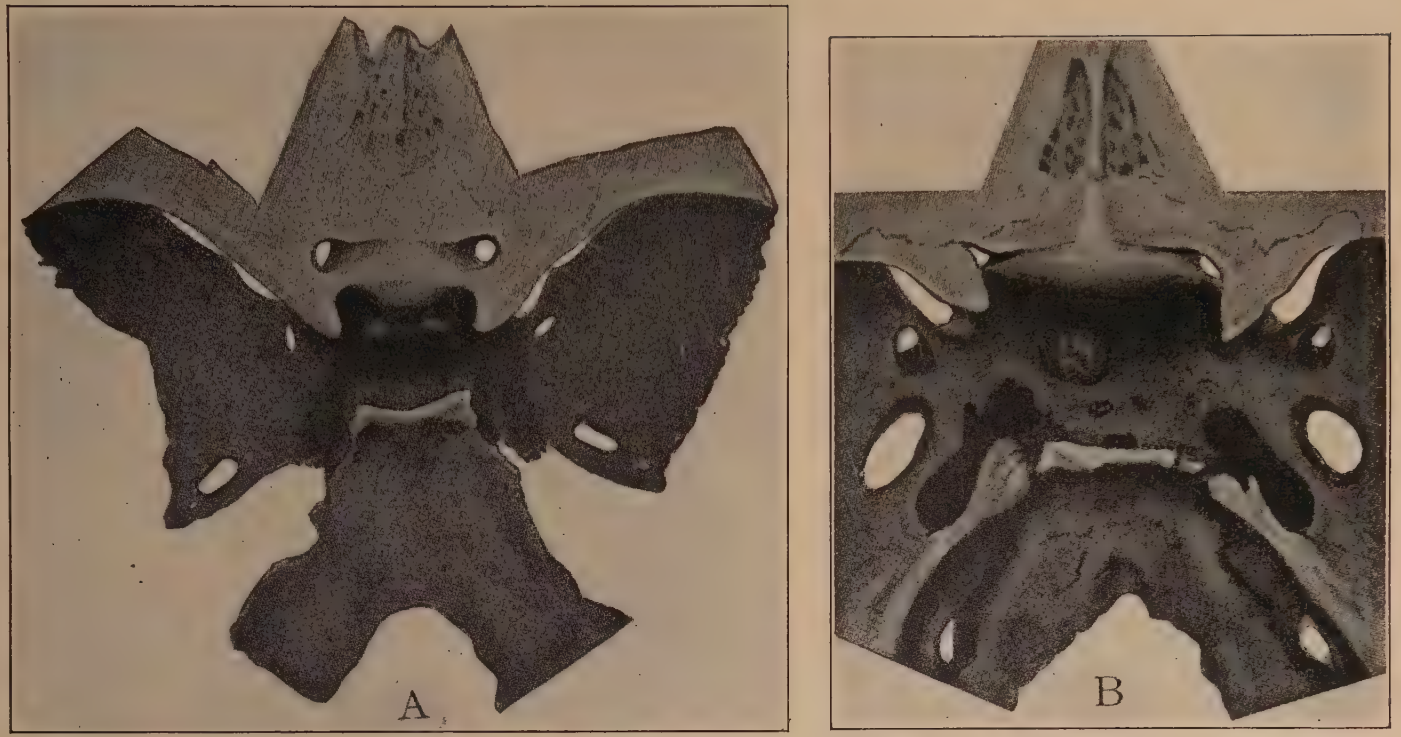


Fig. 19. A. Sella turcica of normal woman. B. Widened sella with bony excrescences in floor in acromegaly. (After W. A. Holden, Arch. Neur. & Psychopathol., 1899.)

frequently postneuritic atrophy and rarely papilledema and non-prominent optic neuritis.

3. Alterations in the visual field for form and colors, concentric contraction, unstable defects, quadrant defects, homonymous and heteronymous hemianopsia and scotomas—central, paracentral and peripheral.

4. Other ocular symptoms which have been described are as follows: visual hallucinations; chromatopsia, especially cyanopsia; persistent photophobia; palsy of various exterior ocular muscles; nystagmus; exopthalmus; thickening and pigmentation of the eyelids with hypertrophy of the palpebral glands."

De Schweinitz agrees with Cushing that in the bitemporal hemianopsia of hypophysis tumor the boundary line is hardly ever regular or vertical and he also has not infrequently encountered homonymous hemianopsia. In all cases the defect for colors preceded that for form. It is important to map the field for all of the usually selected primary colors—blue, red, green—as the defect may at first be present with only one of these colors. In the majority of cases the temporal fields tend to be lost from above downward, the so-called "temporal slant." This is corroborated by Josefson who adds that he has observed that restitution of the fields takes place in the opposite order. The rarity of choked disc in comparison with the frequent optic atrophy is testified to by de Schweinitz, who only once has observed the former in connection with hypophyseal tumor. Rhein found choked disc recorded in four of 169 cases of hypophyseal tumor, 52 of which were instances of acromegaly. Cushing has observed choked disc as a late sign engrafted on the atrophy when the intracranial pressure had reached a high degree.

Of 148 cases of such tumors with disordered fields, studied by Walker and Cushing, 47 had bitemporal hemianopsia, 22 homonymous hemianopsia, and the remaining 79, blindness in one eye. The important lesson from these figures is that bitemporal hemianopsia is by no means the only kind of hemianopsia met with, and that it is only twice as common as the homonymous form. In three cases with homonymous hemianopsia examined post mortem by Cushing it was found that the glandular struma had burst its capsule and extended upward along one side of the chiasma. The hemiopic papillary reaction of Wernicke has been observed by Dodgson, E. Schlesinger, Thomas, and others, but Cushing, on the whole, has found it disappointing. Binasal hemianopsia has been observed by Bittorf and by Fisher. It can hardly be explained by lesion of the chiasma but only by pressure on the outer part of each optic nerve such as might result from bony change about the optic foramina, or rupture of the tumor through its capsule on both sides anteriorly.

The now frequently observed restoration of vision after operation on

the hypophysis confirms the correctness of Cushing's statement that the amblyopia associated with a primary atrophy more often represents a physiological block to light impulses than an actual destruction of the nerves.

Epileptiform Convulsions.—These are not common and are usually explained by the increased intracranial pressure. Grinker's patient early had attacks in which he "held his breath and snored"; later, he had typical grand mal attacks. The hypophysis tumor was large. Roubinovitch relates a case with convulsions. The spinal fluid secured at that time would cause convulsions in guinea pigs while at other times it was non-toxic. "Uncinate fits" with gustatory aura are late symptoms of hypophyseal tumor, and according to Cushing, are more frequent in states of hypopituitarism, such as also occur late in the course of acromegaly. The röntgenologic studies of the sella turcica in epilepsy by McKennan, Johnston and Henninger are interesting in this connection as offering a possible explanation for the occurrence of fits in early cases with hypophyseal and sellar changes but without pressure on the brain.

Pain.—Aside from the "pituitary" and general pressure headache and the pains referable to the articular changes there are other and more obscure pains. Thus, facial pains may be extremely annoying as in the case of Mark; there may be lancinating pains resembling those of tabes, and acro-paresthesias. Sainton and Staté have made a special study of pains in the extremities which they found present in 70 of 140 cases. They ascribed them partly to root irritation by the frequently encountered calcareous or bony placques in the spinal arachnoid. However, in view of the frequency of such placques in various kinds of atrophic conditions of the cord where pain is not a feature this theory is of doubtful value as has been clearly shown by Leopold.

Spinal Cord Complications.—These have been made the subject of special articles by Barrett (1906) and Petrén (1907). Barrett reports a case of old acromegaly in an insane woman of 51 years who was under observation for several years at the Danvers (Mass.) State Hospital. Her sallow skin and general debility suggested pernicious anemia but the blood picture was practically normal. The knee reflexes at first were slightly increased, but later absent. At the necropsy a hypophysis tumor was found as well as marked degeneration in the cervical and upper thoracic cord. It resembled that of pernicious anemia in the absence of involvement of the posterior root fibers and Lissauer's tracts. Previously lighter degrees of posterior column degeneration had been described by Schultze, Duchesneau, Tamburini, Brooks, and Dallemagne.

Petrén devotes himself particularly to the relationship of syringomyelia to acromegaly and rightly points out the weak case made by those who believe they have observed this combination. Usually the trophic changes connected with syringomyelia have been mistaken for acromegaly. Petrén's

own case I, which he claims was the first authentic instance of coexistance of the two diseases, is open to criticism in regard to both diseases. Acromegaly cannot be considered proven, as necropsy showed no hypophyseal changes and the facial bones were not characteristic. The huge hands and feet are partly explained by an existing family tendency to such enlargement, and the presence of an old tuberculosis of the pericardium, tracheobronchial glands, and right lung may have led to a secondary hyperplastic ostitis (Marie's *ostéoarthropathie hypertrophiante pneumique*). The syringomyelia is also doubtful as there was no glia increase, merely epithelial proliferation about the central canal and sclerosis of the neighboring vessels. A case presenting typical clinical and anatomic features of both diseases is that of Bassi, and we are also quite safe in including that of E. Schultz where the acromegaly was complete clinically and anatomically, and the histologic changes in the cord were characteristic of syringomyelia, but there had been no symptoms of the latter except atrophy of some muscles about the shoulder. At all events, the simultaneous occurrence of these two diseases is too rare to be anything more than mere coincidence.

That the much more frequent disease, tabes, should occasionally coincide with acromegaly as in the case of de Castro, is not surprising. Tabes also was present in Levi and Franchini's acromegalic giant (see chapter on Gigantism). There is, however, no reason to suspect that acquired syphilis causes or influences the hypophyseal disease, or that the existence of acromegaly predisposes a syphilitic to tabes. In this connection it is interesting to recall that hypophyseal tumor without acromegalic signs has not infrequently been mistaken for tabes. This has been emphasized by Oppenheim(*b*) (1914). A case in a woman with optic atrophy, loss of tendon reflexes, shooting pains in the legs, and attacks of abdominal pain resembling gastric crises, where necropsy revealed an Erdheim tumor of the hypophysis, has been reported recently by Raulston. But also in typical acromegaly, as pointed out by Oppenheim, this "pseudotabes pituitaria" may exist, evidenced by shooting pains and loss of reflexes, but the characteristic growth disorder here prevents an error in diagnosis. Such a case is reported by Nonne(*a*) in which also the pupils were small and sluggish to light, yet all these symptoms were ascribed to non-tabetic unsystematized cord degeneration.

Differential Diagnosis

Hypertrophic Pulmonary Osteoarthropathy.—This is the one condition for which acromegaly is most likely to be mistaken. It was described and named by Marie in 1890, partly on the basis of cases which he himself had included in his first description of acromegaly. As the name implies,

this disorder affects bones and joints and is associated with pulmonary disease. As originally conceived the bony changes were attributed to stasis and toxemia from obstructive disease of the lungs, but later cases have been described in connection with disease of the heart, liver, and kidneys, and elsewhere (carcinoma of breast, Krüger), and without any discoverable primary disease (Becher). The terms "secondary hyperplastic ostitis" (Arnold(*a*)) and "toxigenic osteoperiostitis ossificans" (Sternberg) have been suggested as more appropriate. However, a survey of the case reports during the thirty years which have elapsed since Marie's discovery shows that some form of pulmonary disease has existed in the great majority of the cases. The importance of the vascular stasis is emphasized in the excellent discussion of this condition by Janeway (1903) in whose cases bronchiectasis existed. The mildest form of the affection is constituted by "drumstick fingers" (*Trommelschlägelfinger*), first described by Bamberger, in which at first only the soft parts are enlarged (clubbed fingers). Later periosteal thickening appears, which does not especially select points of tendinous and ligamentous insertion as in acromegaly. Not only the hands and feet but also the forearms and legs become enlarged so the normal downward tapering of the extremities no longer exists. The nails are very characteristic, being thick, long, brittle and curved like a parrot's beak (*papageienschnabelartig*). In the late stages the soft parts may be actually atrophic. The existence of localized neuritis seems to favor the hyperplastic changes as Möbius(*b*) observed extreme enlargement of the last two fingers following ulnar neuritis in a patient with drumstick fingers secondary to bronchiectasis. The cranial changes of acromegaly are not present. That the two conditions may occur together as has been shown by Braun makes the matter more complicated, and, as Oppenheim states in his

Fig. 20. The elder Hagner. Familial hyperplastic ostitis. (After W. Erb, Deutsch. Arch. f. klin., Med., 1888.)

textbook, further observations are necessary to decide whether a sharp distinction can be made between these two affections.

Familial Hyperplastic and Deforming Ostitis.—We choose this descriptive term in connection with some much discussed and contested cases which possess in exaggerated form the features of hyperplastic osteoarthropathy, also numerous and prominent exostoses, and changes in the soft parts. The onset is soon after puberty, and there is no primary disorder, such as disease of the lungs. Here belong the famous Hagner brothers, first described as "hyperostosis of the entire skeleton" by Friedreich in 1868. (Figs. 20, 21.) Later one of them was included in Marie's first paper on acromegaly but subsequently he considered them as cases of hypertrophic pulmonary osteoarthropathy, while Sternberg refused to classify them under either head. Erb described them as cases of acromegaly, and Arnold, who examined the older brother post mortem, left the question open. In the necropsied case the sella was normal, the upper jaw, but not the lower jaw, enlarged, and there was increased growth of subcutaneous tissue and of hair. Recently Oehme has described two brothers with enlargement of the distal part of the extremities, with unevenness of the bones and numerous osteophytes, thickening of the shafts of the metacarpal bones, thickening of the soft parts at the ends of the fingers and of the skin of the face, no enlargement of jaw, nose or sella. The hairy growth was deficient. A third brother and a sister were said to be similarly affected. As of more distinctly endocrin type we may mention Eulenburg's case of "infantile, familial muscle dystrophy with osteo-arthropathic deformations," and the family described by E. Kretschmer, several male members of which showed enlargement of hands and feet, one with ununited epiphyses at thirty years, tendency to arthropathies of the spine and knees, mental deficiency,

Fig. 21. The younger Hagner. (After W. Erb, Deutsch. Arch. f. klin. Med., 1888.)

eunuchoidism, and in one member, features of muscular dystrophy. Further interest is lent to this familiar group by Janeway's observation that a familial tendency existed in several of the reported "primary" cases of osteoarthropathy.

Ostitis Deformans.—Paget's disease also causes bony enlargement and deformity, but of a different type. The cranial part of the skull is thickened rather than the facial, and the bones of the arms, forearms, thighs and leg are affected instead of the hands and feet. The excessive curving of the long bones seen in ostitis deformans does not occur in acromegaly while kyphosis is common in both. Enlargement of soft parts is not a feature of ostitis. The bony enlargements of acromegaly are usually symmetrical, those of ostitis often very asymmetrical. The onset in ostitis is usually at much later age, after fifty years.

Hemihypertrophy (see section on Gigantism) is sometimes wrongly designated "unilateral acromegaly." It is congenital, involves the whole lateral half of the body and should not offer any diagnostic difficulty.

Syringomyelia.—This condition may be associated with arthropathies, and hypertrophies of bone and soft parts, especially of the hands, but the presence of dissociated sensory disturbance, muscular atrophy and altered reflexes and absence of the acromegalic facies usually quickly settle the question. We cannot subscribe to Vincent's statement that syringomyelia may give rise to the *typical* clinical and anatomical findings of acromegaly.

Exophthalmic Goiter.—At first thought exopthalmic goiter will not be considered a possible source of error as there is a tendency to increased delicacy and slenderness, especially of the fingers, rather than to enlargement. However, in early acromegaly the sweating, exhaustibility, and frequent exophthalmos and thyroid enlargement have occasionally led to an erroneous diagnosis of Graves' disease. Impairment of vision is not a feature of the latter, and tremor and tachycardia are uncommon in acromegaly.

Myxedema.—Difficulty in diagnosis may be encountered in an early case of myxedema. There is no bony enlargement, particularly no prognathism, and the skin, while thick, is smooth and of a different appearance from the rough, wrinkled, redundant skin in acromegaly.

Prognosis

With the exception of the transient and incomplete acromegaly sometimes observed in pregnancy the condition is a permanent and indelible one. However, as has been pointed out, the active process may cease at any stage and the condition remain stationary without any material discomfort and shortening of life. Remission lasting for many years may also occur. Acceleration of the disease may follow pregnancy, trauma, or

fright. The duration of the disease varies from a few years to fifty or more. Victims of acromegaly have been known to reach the age of a hundred years (Léri). In a general way, the later and the more gradual the onset, the more benign the case is likely to be. Most authors (after Sternberg) distinguish an acute, malignant form, fatal in a few years, the ordinary chronic form, fatal in eight to thirty years, and a benign form which does not shorten life. Marked brain tumor symptoms and association with severe diabetes or myocarditis are especially unfavorable.

Treatment

As the disease is subject to spontaneous arrest and prolonged remissions great care is necessary in judging the value of the therapeutic agencies employed. It is especially important to know whether active hyperpituitarism existed at the time a given treatment was given. Much bewilderment results if this point is not borne in mind.

Methods of Treatment.—*Glandular Treatment.*—The use of preparations of the whole hypophysis or of anterior lobe is obviously contraindicated during the active stage if the present views of pathogenesis are correct. The reported good results are to be explained on the ground that the patients at the time of treatment had passed through the not infrequent transition to a state of diminished glandular activity. Our hopes of the discovery of a potent "hypophysectotoxin" or "antihypophysin" have not yet been realized. Aggravation of the symptoms from pituitary treatment should logically be expected, and has actually been reported (J. Salomon, Rénon and Dellille). Salomon's patient who was made worse by pituitary treatment improved on thyroid, and others have reported good results with this gland (results compiled by Hinsdale) while on the other hand increased weakness and glycosuria have been attributed to it (Sternberg). Ovarian treatment to the extent of 5200 tablets was credited with great subjective improvement and reduction in the size of the fingers by Bab, who achieved still further success in his case by implantation of ovaries from a case of osteomalacia. This is at least theoretically sound since there is ovarian deficiency in acromegaly and since osteomalacia in many ways is the antithesis of acromegaly. Kalledey reports return of menstruation and conception after three months of ovarian treatment. Potassium iodide was long ago recommended because it had been useful in goiter and good results have been reported (Sternberg, Fürth). Altogether no conclusions can be reached as to the value of any glandular or drug treatment up to the present time as the results are contradictory and the reported successes subject to heavy discount on account of the laws of coincidences and optimistic suggestibility in both physician and patient.

Röntgenologic Treatment.—The idea of diminishing growth and

hyperactivity of the hypophysis by means of the X-ray is theoretically sound, and recent technical advances have rendered this treatment practicable. It was introduced by Gramegna in 1909. He gave two weekly treatments, directing the rays to the sella turcica through the mouth. After eight treatments there was less headache and improvement in vision but later the condition grew worse and renewed treatment was futile. On account of the insufficient space between the teeth Béclère devised a special method of passing the rays through the frontal and temporal region

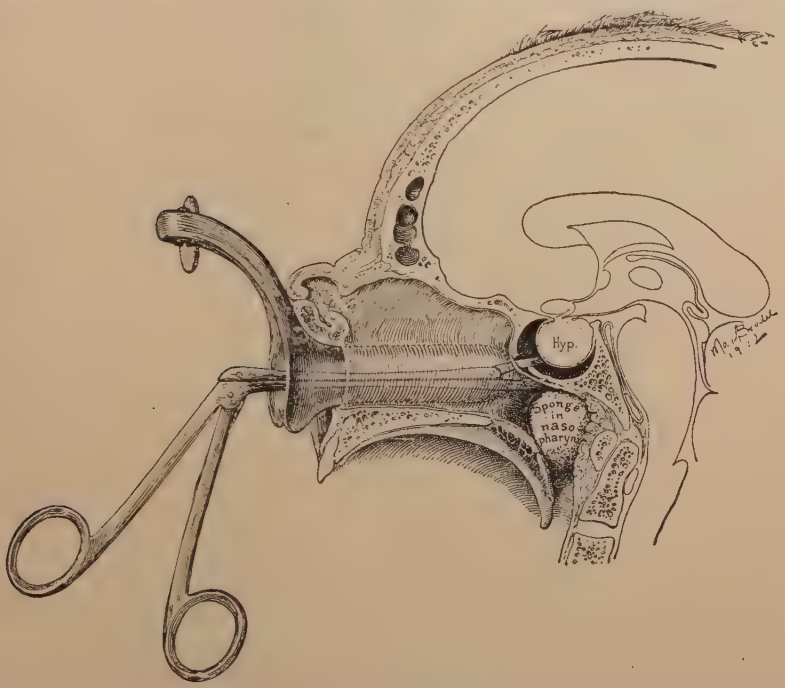


Fig. 22. Approach to hypophysis by infranasal method. (After Harvey Cushing, J. Am. M. Assn., 1914.)

which now is generally employed. The numerous reports of marked improvement of the visual fields as well as of subjective symptoms are encouraging and to a considerable extent convincing, allowing for the factors mentioned in connection with the glandular treatment. Among the most convincing and objective reports, in addition to Béclère's, are those of Jaugeas(*b*), Küpferle and v. Szily, Schäfer and Chotzen, Cavazzeni, and Webster. The treatment is more efficient after an operation on the sella has been performed since much of the bony resistance to the rays then is done away with. Radium is recommended together with the X-rays by Küpferle and v. Szily who also advise the internal administration of iodin preparations during the treatment.

Surgical Treatment.—Here we are no longer dealing with mere theo-

ries, hopes and expectations but with positive results which cannot be challenged on the ground of coincidences and optimism. There is no more inspiring chapter in surgery than the history of the conception and perfection of the methods by which the exposure and removal of hypophyseal tumors are now accomplished with an operative mortality of less than 10 per cent though with a small proportion of cures or of decided or rapid improvement. The idea of reaching the hypophysis surgically originated with Horsley, who first performed the operation on animals (1886). Caton and Paul (1893) and later Horsley attempted unsuccessfully to remove hypophyseal tumors through the middle fossa of the skull. Rapid strides

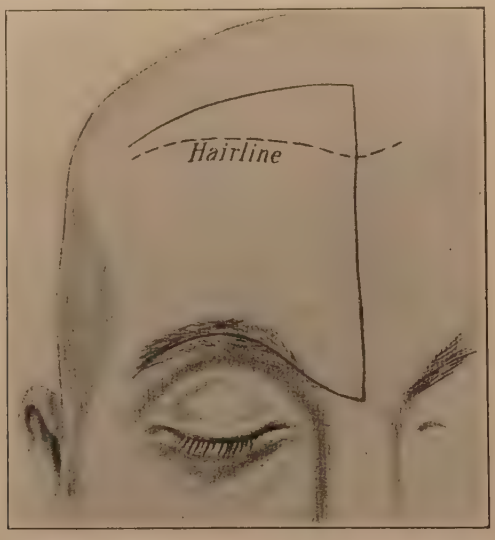


Fig. 23. Line of incision in fronto-orbital approach to hypophysis. (After C. H. Frazier, Surg. Gyn. & Obst., 1913.)

were made after Schloffer(*a*) in 1906 devised a superior nasal approach by which the nose was turned aside and extensive bone resections made so as to open a path to the sphenoidal sinus and thence to the sella. This method, although improved by Hochenegg(*b*) and v. Eiselberg, has been practically discarded as unnecessarily mutilating, in favor of the inferior nasal method proposed by Kanavel and modified by Hirsch(*b*), Halstead, and Cushing(*e*). (Fig. 22.) In its perfected form, as described by the last named author (1914), the main steps are as follows: The upper lip is drawn up, and a transverse incision about 2 cm. long is made across the frenum down to the bone. When the septum is reached the mucous membrane is separated on each side, the septum resected, and after enlarging the passage thus procured, by means of dilating plugs, a bivalve speculum is introduced. A headlight is now used and by means of rongeur forceps the anterior wall of the sphenoidal sinus is bitten through. Next,

the roof of the sinus, which is also the floor of the sella, is similarly removed piecemeal and the dural capsule of the hypophysis comes into view. This is incised, and the conditions encountered will then decide the further procedure. A cyst may be incised, or a hypophyseal tumor removed piecemeal, or nothing further done, the operation in the latter instance constituting a "sellar decompression."

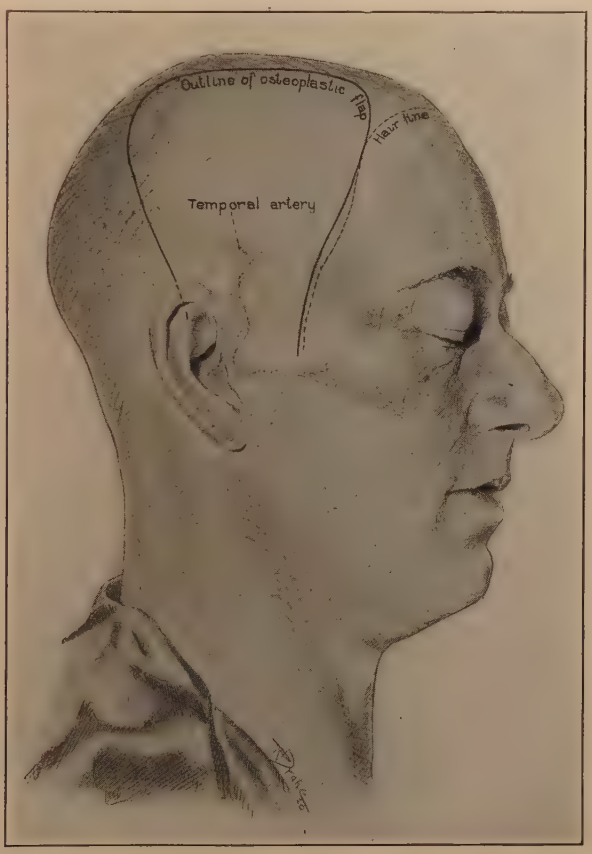


Fig. 24. Adson's incision for approach to hypophysis through anterior fossa. (After A. W. Adson, J. Am. M. Assn., 1918.)

During the period in which the transsphenoidal methods were perfected other surgeons sought a safe and practicable intracranial route of approach. The temporal route having proved too difficult Krause (1905) proposed a frontal one, through the anterior fossa. The method was successively improved by McArthur, Bogojawlensky, and Frazier, and brought to the highest perfection by Adson. While Frazier carried his incision as far forward as the median line of the forehead and resected the orbital roof (Fig. 23) Adson makes his flap farther backward (Fig. 24), and

opens the dura widely so as to expose the frontal lobe. With the patient almost in a standing position and head held back the frontal lobe is allowed to gravitate out of the anterior fossa and is protected by imbricating layers of rubber tissue. The chiasma and hypophysis are brought into view quite readily, and a tumor of the latter may be removed in toto by means of a snare. The advantages claimed by Adson for this operation are: "1. Its approach presents a dry field, free from infection, in which it is comparatively easy to expose the optic commissure and the tumor. 2. The expos-

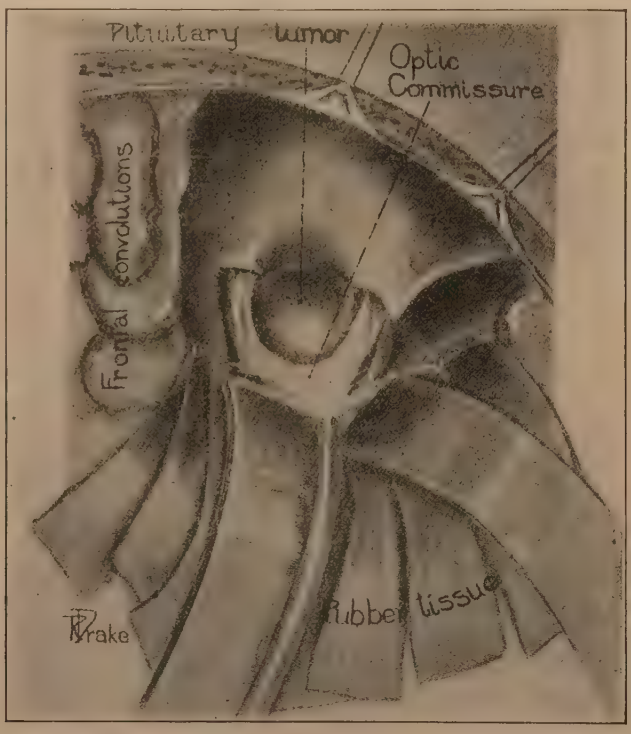


Fig. 25. Exposure of hypophyseal tumor by intracranial method. (After A. W. Adson, J. Am. M. Assn., 1918.)

ure permits the dissection of the tumor from the optic nerves and the commissure and the removal of all or any portion of the tumor and pituitary body that is desired. 3. Trauma of the commissure and nerves is prevented, as the sponging is done against the floor of the sella instead of working upward against the commissure and nerve peduncles."

Indications for and Choice of Operation.—Signs of involvement of the optic nerves and persistent, severe headache when not relieved by X-ray treatment, or showing no tendency to spontaneous disappearance, call for surgical relief. In early acromegaly the tumor is likely still to be within the sella, and the headache to be caused by distention of the dural capsule

of the hypophysis, hence little or no relief is to be expected from a simple subtemporal decompression. Sellar decompression with or without removal of tumor tissue naturally suggests itself. If skiagraphic appearances indicate that the tumor already is largely above the sella, an intracranial approach such as that described by Adson would seem more

Fig. 26. Placing the snare about the pedicle of the hypophysis tumor. (After A. W. Adson, J. Am. M. Assn., 1918.)

rational in that it enables the surgeon to survey the structures involved and work more in the open than by any of the transsphenoidal methods. If general brain tumor symptoms are marked and there are signs of pressure on the motor nerves of the eyeballs or on the cavernous sinus, perhaps with choked disc superimposed on the previous optic atrophy, a subtemporal decompression or a callosal puncture may be the only procedure justified. If this causes decided improvement in the general condition a radical operation, preferably by the intracranial route, may be performed later.

Dystrophia Adiposgenitalis . . . . . *Harvey G. Beck*

Definition — Introductory — Historical — Experimental Research — Pituitary Feeding—Neighborhood Signs and Symptoms—Ophthalmic Findings—Alterations in the Sella Turcica—Skeletal Undergrowth and Infantilism —Genital Hypoplasia—Polyuria—Cachexia Hypophysopriva—Adenoids and Pituitary Deficiency—Illustrative Cases—Symptomatology—Etiology —Diagnosis—Prognosis—Treatment.

Dystrophia Adiposogenitalis

HARVEY G. BECK

BALTIMORE

Fröhlich's Syndrome. Adipositas cerebralis. Hypophyseal dystrophy. Hypopituitarism. Hypophypophysismus. Syndrôme hypophysaire adiposogénital (Launois and Cléret). Degeneratio seu dystrophia adiposo-genitalis (Bartels(*b*)).

Definition

A condition due to underfunction of the hypophysis, characterized by obesity, genital hypoplasia and faulty skeletal development; associated with nervous and mental symptoms which are either the direct result of deficient secretion or dependent upon local or general intracranial pressure.

Introductory

In considering the clinical phases, which manifest themselves as the result of disturbances of the glands of internal secretions, it is necessary that one should have a clear conception of the normal functions in order to properly interpret the significance of the various clinical syndromes caused by the deviation of their respective functions from the normal. The remarkable strides, recently made in the study of endocrinology, can be attributed largely to the development of a better knowledge of the physiological activities of the various glands by means of animal experimentation, feeding of gland substance, and clinical observation. This is of special significance inasmuch as a diagnosis is established on a functional basis rather than on a pathological-anatomical basis.

The pituitary has become recognized as one of the most important, if not the most important, gland of the endocrin system. The gland is composed of two lobes, which differ from one another embryologically, histologically, and functionally. Disturbance of function may give rise to certain syndromes depending upon

1. Over-function—hyperpituitarism (acromegaly, gigantism)
2. Under-function—hypopituitarism (dystrophia adiposogenitalis)

3. Absence of function—apituitarism (cachexia hypophysopriva)
4. Perverted function—dyspituitarism (mixed symptoms)

Besides alteration of function leads to compensatory disturbance in other endocrin glands (thyroid, gonads, adrenals) with symptoms referable to these organs; a condition which naturally tends to a more or less complex symptomatology.

However, dystrophia adiposogenitalis, with which this chapter has to deal, is a well defined syndrome, paralleling in many respects that of myxedema and cretinism occurring in thyroid deficiency, and when uncomplicated can be easily recognized.

Historical

The earliest observation showing the effect of an arrested endocrin function upon the body is that of the eunuch, which dates to antiquity. The changes in skeletal formation, the abnormal distribution of fat, and the faulty development of the secondary sex characters, due to loss of function of the sex glands, has been well known. Owing to the lack of knowledge concerning the physiology and pathology of the glands of internal secretion no relation between the loss of function and fat dystrophy in other than the sex glands had been suspected. However, in 1883 both Reverdin and Kocher conclusively demonstrated such a relation with the thyroid by complete extirpation of the gland, and in 1901 Fröhlich(*a*) described his epoch-making syndrome of hypophyseal deficiency in which obesity and genital hypoplasia were the most striking symptoms.

Fröhlich's case was that of a boy fourteen years of age, who had suffered two years with headache and vomiting, and had gained weight rapidly. The fat was distributed in a characteristic manner, the genitalia were undeveloped, and the pubic and axillary hair was absent. To this clinical picture Bartels(*b*) later gave the name of dystrophia adiposogenitalis. Other cases of obesity with features embraced in the above syndrome, however without reference to the hypophysis, had been described previously as cerebral adiposity (Schuster).

Dr. Garrison of the Surgeon General's library, after reviewing the history of the subject stated that possibly the earliest case of true hypophyseal obesity described prior to Fröhlich's was reported by Barnard Mohr in 1840 (Wochenschr. f. d. ges. Heilkunde, Berlin, 1840, VI, 565-571). It is interesting to note that in the same volume Basedow's remarkable description of goiter appeared. Mohr's patient was a woman forty-seven years of age with sarcoma of the hypophysis. The chief symptoms were visual disturbances, vertigo, periodical headaches, clumsy movements, mental deterioration terminating with symptoms of apoplexy. An unusual obesity developed with extraordinarily large abdominal di-

mensions, especially in the transverse diameter. The autopsy showed a very large degenerated pituitary gland, an enormous deposit of subcutaneous fat with an increase of fatty tissue in the heart, liver and mesentery.

Ocular symptoms were recognized long before obesity as a feature of pituitary disease. Thus Vieussens as early as 1705 reported a case of tumor of the hypophysis with amaurosis, and Ward (1823) and Hedlund (1833) each reported a case of tumor with total blindness. Harvey (1855) mentions a sudden and complete amaurosis as the result of a pituitary abscess and a scrofulous tumor compressing the optic nerve. Optic neuritis and bilateral abducent paralysis occurred in a case of Leber's (1866) with gliosarcoma of the infundibulum and tuber cinereum.

Numerous cases of pituitary disease were described before Mohr's report; none of them, however, correspond as closely to Fröhlich's syndrome. These reports deal more especially with the pathological anatomy, although as a composite practically all the important clinical manifestations are embraced which comprise the symptomatology of dystrophia adiposogenitalis. A comprehensive review of the subject of pituitary lesions was published by Rayer in 1823; in addition he cited four cases and reported one of his own. He called attention to the fact that Wepfer (1734) had observed a change in the size of the gland, and Petit (1718) found the gland "squirrheuse" in most individuals with hydrocephalus. Morgagni (1766) mentions a case in which the gland showed a light yellow tint and others containing considerable mucoid material. Glands containing concretions were reported by Vicq-d'Azyr (1779) and Bichat. The latter also mentions a scirrhous condition and suppuration. Among others Rayer quotes Chaussier (1812), who reported enlargement of the pituitary, and Baillie (1815) and Rullier (1823) and others who mentioned amaurosis as a symptom of pituitary tumors. His personal observation (1814) was that of a man 47 years of age, who gradually became lazy and careless, and developed mental retardation, frontal headaches, failing *vision* terminating in total blindness, constipation, vomiting, stupor and *slow pulse*. Rayer in portraying the mental condition of this patient gives a classical description of *narcolepsy*, a symptom occurring in advanced hypopituitarism. At autopsy a pituitary tumor was found an inch and a half in diameter. The adipose tissue, although not abundant, was described as being very yellow and resistant, and the omentum contained very yellow and solid fat.

The case reported by Ward (1823), previously mentioned was somewhat similar. The patient was a man 38 years old, who had a large pituitary tumor pressing on the optic and olfactory nerves causing *blindness*, headache and a condition of stupor and *somnolence* of the same type above mentioned.

Raymond Vieussens (1705) reported the case of "Le Cardinal de Bonsy", who died at the age of 72 from a tumor of the pituitary gland the size of a hen's egg; there was also softening of the brain. For eleven years he suffered periodically with *epileptiform seizures* affecting the eyes, lips and tongue. He developed *amaurosis* in the left eye and impairment of memory, and died from an apoplectiform attack.

A case of an *inflammatory tumor* of the pituitary, which also involved the left lateral and middle fossae of the skull, occurring in a woman 38 years of age, was reported by Lévêque-Lasource (1808). The chief symptoms were *acute headache with vertigo,* fatiguing sleep, "painful" dreams, *blindness* in both eyes, stupor and coma. The pituitary was twice the normal size and contained numerous puriform foci of a fetid odor.

An interesting case of pituitary disease, especially from the standpoint of treatment, is one studied by de Haen 1759-61 (cited by Rayer). This was probably the earliest case reported in which amenorrhea was associated with pituitary lesion. The patient was a girl 20 years old with a history of *amenorrhea* for three months, habitual vomiting for fourteen days and *amaurosis;* symptoms which disappeared after the judicious employment of purgatives. Later menstruation again ceased; vomiting and amaurosis reappeared; and as purgatives did not relieve her this time the actual cautery was applied to the left side of the head with the result that she died in five days from symptoms of meningitis, which the author attributed to the use of the cautery. The autopsy showed a left-sided meningitis, and the vessels, especially those distributed to the left hemisphere, contained a large quantity of *air* (probably gas bacillus infection). The infundibulum was enlarged 8 or 9 lignes (2 cm.) in diameter and contained pultaceous material and calcareous matter. This lesion caused pressure on the chiasm.

Other cases have appeared in literature prior to Mohr's but without a description of obesity resembling the hypophyseal type. However, symptoms of hypopituitarism are enumerated, including *visual defects, mental disturbances, amenorrhea, epileptic seizures, obesity, slow pulse, stupor* and *coma.* Obesity as a symptom was mentioned by Morgagni in 1766; pituitary changes with epilepsy by Greding in 1781 and also by Wenzel in 1810, the latter attributing the origin of epilepsy to the pituitary gland which he considered had a very important function. In addition Wenzel called attention to the enlargement of the sella in pituitary lesion. Rogowitsch (1886) noted hypertrophy of the pituitary after removal of the thyroid. A great advance was made by the introduction of X-ray as a means of diagnosis by Oppenheim in 1889. Kollarits (1905) reported from the literature up to 1904 fifty-two cases without acromegaly ten of which appeared after Fröhlich(*a*) published his case (Touche '02, Vassale '02, Carbone '02, Finkelnburg '02, Köster '02, Neuman '02, Ces-

tau & Halberstadt '03, Zak '04, and two of his own). However, he did not mention Berger's which was similar to Fröhlich's, and which was reported soon after the latter published his case. Uhthoff(*b*) (1915) collected forty-four cases with affection of the pituitary, chiefly tumors, which appeared in the literature prior to 1886, the year in which Pierre Marie described the syndrome of acromegaly. From this period to the time of the report of Fröhlich's case (1901) pituitary tumors were roughly classified into two groups—those with symptoms of acromegaly and those without symptoms of acromegaly. There was apparently considerable confusion as to the nomenclature until Bartels(*b*) (1908) suggested the term dystrophia adiposogenitalis. Hitherto the vast majority of cases of pituitary disease were reported as acromegaly. Since then hypopituitary states —dystrophia adiposogenatalis, pituitary infantalism, cachexia hypophysopriva—have been more generally discussed. Uhthoff(*b*) later collected three hundred and twenty-eight cases of pituitary disease reported prior to 1911, including the forty-four above mentioned. Of these two hundred and seven presented symptoms of acromegaly and one hundred and twenty-one were without symptoms of acromegaly.

At a meeting of the Ophthalmological Society of the United Kingdom in 1887—long before the syndrome dystrophia adiposogenitalis was recognized—there occurred a remarkable discussion on the subject of pituitary lesions in their relation to the eye symptoms, obesity, menstrual disturbances and mental manifestations. The following is quoted from the proceedings of this meeting published in the British *Medical Journal,* Vol. I, 1887, p. 1334.

Mr. J. B. Story (Dublin) read an account of the case of a young woman who gradually became blind in the right eye, and had temporal hemianopsia in the other eye. She suffered from headache and slightly from vomiting. One of the things she complained most of was drowsiness about midday each day. It was noticed that she got much stouter. She also suffered from irregular menstruation. At the time of reporting the case she was in fair general health, and able to follow her occupation (that of a dressmaker).—Mr. Nettleship remarked that a very similar case had been recorded in the Society's Transactions, and in that instance, after death, a tumor was found in the pituitary fossa. Other similar cases had been published, and he had lately seen a case at St. Thomas's Hospital where the same train of symptoms had been produced in the same way.—Dr. Hill Griffith said that he had placed on record a case identical with that of Mr. Story. Cessation of menstruation and sleepiness had been present in his case; and, in several cases that he had seen, the patients had complained of getting stout.—Dr. James Anderson briefly described the case he had published, which closely agreed with that of Mr. Story. He said that it was the rule in pituitary tumors that the patient should get very stout.—Dr. Coupland mentioned also the concurrence of an increased

development of fat in conjunction with disease or enlargement of the pituitary body.

The hypophyseal origin of obesity was not generally accepted until Cushing(*b*) and Aschner(*a*) by their experimental investigations successfully demonstrated that obesity as well as genital hypoplasia develops in hypophysectomized animals.

Experimental Research

Victor Horsley as early as 1885 attempted the experimental removal of the pituitary gland in animals. His experiments were followed by Dastre '89, Gley '91, Marinesco '92, Vassale and Secchi '94. The results of these experiments on the whole were unsatisfactory, most of the animals dying immediately after operation, and no data of any clinical value were obtained.

It appears that no further investigations along this line were made in the study of the pituitary function by extirpation of the gland until Caselli and Friedmann and Mass in 1900 and Vedova in 1903 made similar experiments, which also proved unsuccessful. These investigators employed chiefly the nasal or temporal route as their method of operative procedure.

By means of a new method known as the bitemporal, and possibly better technique, Paulesco(*b*) (1906), assisted by a surgical colleague, was the first to succeed in hypophysectomizing animals which survived the operation.

These experimental studies were soon supplemented by the brilliant researches of Harvey Cushing and his co-workers (1909 & 1910). Silbermark (1910), Biedl(*b*) (1910), Ascoli and Legnani (1912) also conducted successful experiments and confirmed the findings of Paulesco and Cushing, the results of which can be summarized as follows: Removal of the whole gland is uniformly fatal, producing symptoms of tremor, muscular fibrillation, diminution of pulse and respiratory rate, subnormal temperature, stupor and coma (cachexia hypophysopriva acuta). Removal of the posterior lobe does not cause death or any special symptoms. Complete removal of the anterior lobe results in death to the animals. Separation of the stalk causes death. Partial removal of the anterior lobe causes obesity. Cushing and his collaborators made the additional observation that the obesity was of the character found in the condition described as dystrophia adiposogenitalis since it was associated with genital atrophy; and they further observed that in young animals persistent infantilism occurred after partial removal of the anterior lobe. The same observers also noted that the subnormal temperature, which is a symptom in dystrophia adiposogenitalis, could be raised by an injection of an extract made from the pars anterior. This phenomenon they referred to as the "thermic reaction."

The increased carbohydrate tolerance, studied by Goetsch, Cushing and Jacobson, and the low blood pressure, symptoms of posterior lobe deficiency, they were able to relieve by injection of infundibulum.

W. Blair Bell(*b*) in some recent animal experimentation, was unable to produce the syndrome of dystrophia adiposogenitalis by the partial removal of the pars anterior, although it followed compression and separation of the stalk; however, in both instances the genital syndrome developed.

Pituitary Feeding

For a complete and up-to-date bibliography on the effect of pituitary feeding the reader is referred to the admirable article of Hoskins and Hoskins (1920), Endocrinology, Vol. IV, No. 1, p. 30. After a careful analysis of the results obtained by many investigators, including their own studies, they make the following statement: "From 1897-1916 there was about an even division of opinion as to whether pituitary feeding would or would not give positive results, but since then most of the papers published on the subject agree that at least with the feeding of the anterior lobe of the hypophysis a definite stimulation of growth can be produced. This has been claimed for protozoa (Flatcher '19), worms (Wulsen '16), birds (Winternitz '16 opposed by Pearl '16) and mammals (Robertson '17 and Marinus '19)."

Goetsch(*a*) ('16) made extensive investigations on the effect of pituitary feeding upon growth and sexual development in rats. Feeding of the anterior lobe extract caused increased weight and greater and more vigorous body growth and development over the control. The period of complete sexual development is shortened by at least one-third of its normal time, and the sexual instincts are early awakened. The posterior lobe extract causes failure to gain in weight, loss of appetite, increased peristalsis, muscular tremors and weakness in the hind legs.

Grafting.—Numerous attempts to transplant the hypophysis with the aim of increasing functional activity have met with failure. Schaefer repeatedly implanted the whole organ or small portions into the tissues of white rats, rabbits, and guinea pigs without satisfactory results.

Exner states that he was able to observe a temporary increase of growth in non-hypophysectomized rats over their controls, in which he implanted an extra pituitary.

Crowe, Cushing and Homans(*a*) were able to prolong the life of the dogs in which the whole gland was extirpated, but they were unable to save them. They admitted that the results may have been due to absorption of the secretions contained in the implanted gland. However, a successful graft from the pituitary of a child dying in childbirth was made by Cushing(*b*) in a man suffering from destruction of the gland through cystic de-

generation. The patient showed symptoms verging on cachexia hypophysopriva but was kept alive on daily injections of whole gland extract until the gland was implanted in the subcortical tissues of the temporal lobe by which he was permanently benefited.

Pharmacological Researches.—One of the most important contributions to the study of the pituitary gland was by Oliver and Schäfer in 1895. These observers demonstrated by intravenous injection of an extract of the whole gland that it contains a pressor substance, causing a rise in blood pressure, thus establishing one of its physiological functions.

Howell(*b*) in 1898 found that this substance resided in the posterior lobe (pars nervosa and pars intermedia) and that anterior lobe extract had no such effect. Moreover he observed that it exerted an inhibiting influence on the heart's action. Shäfer and Swale Vincent in 1899 confirmed Howell's experiments and further determined that its action on the heart and blood vessels was through the peripheral mechanism. A detailed description of its pharmacological properties will be found in the chapter on Physiology of the Pituitary Gland.

T. Brailsford Robertson(*e*) (1916) isolated from the anterior lobe of the pituitary body a lipoid, which contains a growth controlling principle. To this substance he gave the name Tethelin. It comprises about 0.7 per cent of the fresh anterior lobe tissue and contains phosphorus and nitrogen in the proportion of 1:4. The administration of tethelin has the same effect upon growth as anterior lobe extract.

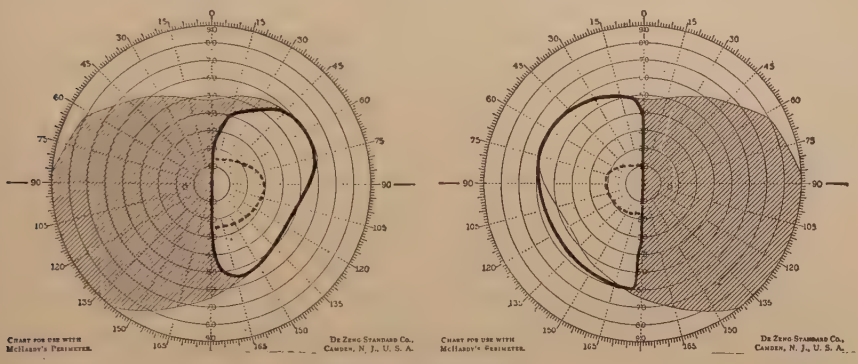
From the foregoing it will be observed that animal experimentation, feeding of pituitary gland substance, grafting methods, metabolic studies, and pharmacological researches all play an important rôle in establishing the basis of symptoms in dystrophia adiposogenitalis.

Neighborhood Signs and Symptoms

Special Nerve Involvement.—These are due to local pressure, which may involve the cerebrum, the base of the skull and the nasopharynx. Injuries to the cerebral nerves give rise to some of the most important neighborhood symptoms. The nerves which are most liable to be injured are the optic, and the nerves supplying the eye muscles (III, IV, VI). Nerves more rarely injured are the olfactory, trigeminus, and facial.

The Visual Disturbances.—These depend upon optic nerve lesions and lesions of the chiasm, the result of a hyperplastic struma extending beyond the sellar confines or of a primary infundibular growth. Aside from direct pressure a number of authors (Sachs, Berger, Erdheim, Bartels, etc.) partly attribute the effect upon the optic tract to interference with the blood supply. Visual disturbances are the commonest and the

most serious of all local pressure symptoms associated with hypophyseal disease. These lesions are usually bilateral. The most important lesion is primary optic atrophy, in one-third of which choked disc precedes the atrophy. In a series of 183 cases of hypophyseal tumors collected by Walker and Cushing 148 showed disturbance of the visual field, 47 of which manifested bitemporal hemianopsia, and the remaining blindness in one eye. Total blindness in both eyes rarely occurs. Bitemporal hemianopsia, which has been considered quite characteristic of pituitary lesions, occurred in about 32 per cent of cases with distorted visual fields. In 19



(Dotted lines field for red.)

Fig. 1. Mrs. K., age 46 (Jan. 8, 1920). complaining of quivering of the eyes for not more than five years; headaches rarely.

1. Partial atrophy of both optic discs, more marked in right eye.
2. Central vision with correcting glasses (—1.0 Ds- 0.75 Dc ax 90), R.E. 20/76; L.E. 20/24.
3. Marked nystagmus, chiefly vertical, slightly rotatory.
4. Examination of the fields shows sharply divided bitemporal hemiopia passing through point of fixation.
5. The X-ray showed an enlarged sella with symptoms of hypopituitarism.
6. Diagnosis: hypophyseal mass with hypopituitarism of the glandular portion.

(Courtesy of Dr. Harry Friedenwald.)

per cent there were no perimetric deviations noted. The homonymous defects occur relatively infrequent as compared to the bitemporal. Bitemporal hemianopsia may also appear as a symptom of primary disease of the optic nerves, as a local manifestation of cerebral lues or as a symptom of tabes. Early blindness is rare (Leber, Josephson, Henneberg), and in the non-malignant and slowly-growing tumors of the hypophysis or of the infundibulum the visual disturbances appear relatively later, sometimes not for years.

The changes in the visual fields ordinarily progress slowly involving primarily the color boundaries, beginning most frequently in one upper temporal quadrant, which gradually develops into a more or less complete temporal hemiachromatopsia. The color fields are always involved before the form fields.

At a certain stage of the process in the development of bitemporal

hemianopsia, the visual field is bisected by a vertical meridian passing through the point of fixation. This form is supposed to be typical although it is not frequently observed.

The amblyopia associated with primary atrophy shows a tendency to post-operative restoration of vision if the tumor is removed or pressure relieved. As a result of optic atrophy and distortion of the visual fields pupillary abnormalities manifest themselves. The absence of light reflex is either due to loss of vision or oculomotor paralysis.

Exophthalmos of varying degree is present in almost all patients with tumors; it rarely occurs in the absence of growth. It is presumably due to local stasis and not to sympathetic stimulation or an associated hyperthyroidism. An hypophyseal tumor by causing pressure backwards may involve the nerves supplying the muscles of the eyeball causing diplopia. The oculomotor is much more often affected than the abducens. Nystagmus is not uncommon. Uhthoff, previously referred to, collected three hundred and twenty-eight cases of tumor of the hypophysis or hypophyseal region which he studied in reference to visual disturbance. The following tabulation by Uhthoff shows the relative frequency in which various eye symptoms occurred in acromegaly, and hypophyseal lesions without symptoms of acromegaly (hypopituitarism—dystrophia adiposogenitalis).

Ophthalmic Findings

A. DISTURBANCES OF THE BASAL AND PERIPHERAL OPTIC NERVE FIBERS

	I. Affections of the hypophysis without acromegaly.	II. With acromegaly.
1. Amblyopia and amaurosis without definite notes	28.5%	7 %
2. Temporal hemianopsia	31 "	43 "
3. Homonymous hemianopsia	1.8 "	4.1 "
4. Choked disc	12.6 "	5.3 "
5. Optic neuritis	11.7 "	5.3 "
6. Atrophy of the optic nerve	22.7 "	19 "
7. Compression of the chiasm and the optic nerves demonstrated anatomically without note as to visual disturbances	10 "	– "
8. Visual hallucinations	0.8 "	– "
9. Retinal changes	– "	1.9 "
10. Chronic iritis	– "	0.5 "
11. Cataract development	– "	1.9 "

B. DISTURBANCES OF THE OCULAR MUSCLES

1.	Oculomotor paralysis	20 %	11 %
2.	Abducens paralysis	6 "	1.9 "
3.	Ophthalmoplegia	3.4 "	1.5 "
4.	Nystagmus	2 "	5.8 "

Headaches.—Among the initial symptoms of pituitary growth are the periodical headaches, which especially occupy the frontal and temporal regions, and may even extend to the suborbital and to one or the other eyeball (Rosenthal 1879). Headache in some form occurred almost invariably as a symptom in my series of cases. It is often the most annoying symptom. The significance of cephalic pains occurring in hypophyseal tumor was especially emphasized by Cushing(*b*). He differentiated headaches originating in a hyperplastic pituitary gland from those due to intracranial tension. The former he attributed to distention of the glandular envelope because relief of headache immediately followed the splitting of a tense capsule of the gland.

Pardee, who made a careful study of the subject of pituitary headaches, considered that they constitute one of the early symptoms of pituitary disease. Their characteristic features are their location, their duration and persistence, and their relief under specific medication.

The location of the headache is variously described as bitemporal, intratemporal or deep frontal. The patient feels as if it were situated behind the eyeballs, and in endeavoring to locate it usually places the finger on either temple. Firm pressure over the temples may elicit tenderness.

There is a feeling of tension of the eyeballs and a sensation of pressure, distention or bursting ache in the intratemporal area. The headache is usually continuous and lasts from one-half hour to several days—menstrual headaches frequently take on this form. Mental strain, excitement and errors in diet, especially an excess of sugar, are considered predisposing factors; vomiting which occurs occasionally affords relief. These headaches occur in both conditions of hyperfunction and hypofunction of the pituitary gland. Timme(*a*) in his description of a new pluriglandular compensatory syndrome confirms Cushing's and Pardee's view as to the pituitary origin and the location of the headache.

Alterations in the Sella Turcica

Formerly a diagnosis of pituitary diseases was more or less presumptive unless röntgenographic studies revealed some anatomical alteration in the size, shape, and general outline of the sella turcica. This, of course, was due to the fact that the clinical syndromes associated with the disturbance of the various functions of the gland were not as well defined and as thoroughly established. It is now well known that even marked

cases of hyperpituitarism (acromegaly and gigantism) or hypopituitarism (dystrophia adiposogenitalis) may occur without demonstrable sellar deformation, and, that in a considerable proportion of cases of hypophyseal dystrophy no X-ray evidence of sellar bone lesion is found.

However, the recognition by means of X-ray of structural alteration of the sella turcica is of great importance, especially in distinguishing the neoplastic from the aneoplastic form of the disease.

X-ray Sella.—In order to determine what constitutes a pathological abnormality in the size, shape and general outlines of the sella turcica,

Fig. 2. Sella normal in size and general outline. (Röntgenogram by Dr. John Evans.)

one must be familiar with its normal anatomical outline and dimensions and the normal variations. Keith's skeletal measurements for the normal sella average 10-12 mm. anteroposteriorly, 14-15 mm. transversely and 8 mm. in depth. Profile radiographic measurements exceeding 15 mm. anteroposteriorly and 10 mm. in depth may be looked upon as indicating an enlargement (Cushing). For a detailed and comprehensive study of the anatomical outlines and measurements of normal sellæ of different ages with their average dimensions, Schüller's treatise should be consulted.

Oppenheim(*a*) (1899) was the first to make a diagnosis of hypophyseal tumor in a case of acromegaly by means of the X-ray. The röntgenogram showed a widening of the sella turcica. Important contributions to the

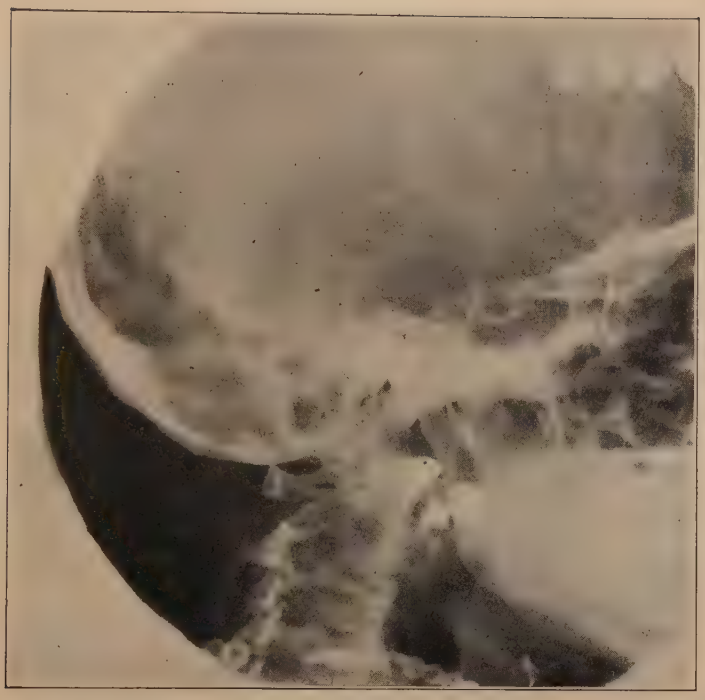


Fig. 3. Closed-in type of sella due to thickening of both anterior and posterior clinoid processes.

CHIEF SYMPTOMS: obesity and amenorrhea. (Röntgenogram by Dr. John Evans.)

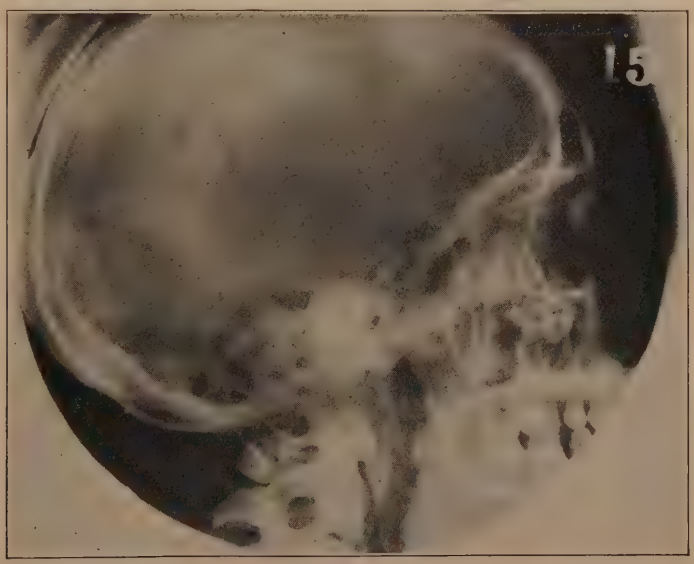


Fig. 4. Closed-in, flattened sella, prolongation of anterior and posterior clinoid processes. (Note separation of teeth.)

GROUP A, CASE IV. Dystrophia adiposogenitalis. Girdle type of obesity. Fat redistributed and body configuration restored to normal by treatment. (Röntgenogram by Dr. John Evans.)

study of this subject have been made by Fuchs, Erdheim(*b*), Jaugeas(*a*), Kohler, Fisher, and Schüller (the latter's treatise on Röntgen diagnosis of the head, containing a complete bibliography, was recently translated into English). By means of the character of sellar deformation Erdheim's investigations made it possible to distinguish between intrasellar—true hypophyseal—and extrasellar growths. In the former group the pituitary fossa becomes enlarged in all diameters; in the latter group in which the tumors develop above the sella there is only widening to the entrance of the fossa. However, both types are subject to variation in minor de-

Fig. 5. Slightly enlarged sella of normal variation. (Röntgenogram by Dr. John Evans.)

tails, depending upon the size, location, and direction in which the growth proceeds. Erdheim states that acromegaly is most frequently associated with the former lesion and dystrophia adiposogenitalis with the latter.

Cushing(*b*) distinguishes three types of pathologically deformed and enlarged sellæ.

1. Those associated with thickening of the clinoid processes and dorsum ephippii.
2. Those with thinning from pressure absorption of these parts.
3. Those with more or less destruction of all outlines.

In the first variety the enlargement is accompanied by thickening of the walls. The type is confined to the hyperpituitary cases and the bony

thickenings are probably due to osseous overgrowth, a feature of acromegaly and gigantism. In the second variety there is thinning with perforations of the sellar floor as well as of the dorsum, which is caused by bone absorption from pressure atrophy. The bony capsule may become too thin to cast a very definite shadow. The condition occurs in advanced hypopituitarism. In the early cases there may only be a simple spherical distention. In the third variety the dorsum is almost completely absorbed, the floor pushed downward and the bony landmarks, with the usual exception of the anterior clinoid processes, destroyed.

Fig. 6. Large, open sella. Case of acromegaly and gigantism with secondary hypopituitarism. Absorption of the dorsum and posterior clinoid process. (Röntgenogram by Dr. John Evans.)

To another important group, to which Cushing(*b*) called attention belong the abnormally small sellæ which accompany the primary glandular hypoplasia of the young; a condition frequently associated with dystrophia adiposogenitalis and infantilism.

Some interesting radiographic studies of the sella turcica in its relation to epilepsy and hypopituitarism have recently been made by Johnston. In a series of more than 100 cases of epilepsy studied he found alterations in the sella in a certain group which occurred between the ages of 15 and 35 with an uneventual history. "The changes consisted for the most part in an overgrowth of the anterior and especially the posterior clinoidal processes, which in addition to an increase in area and length were slowly folded over and down upon the pituitary gland enclosing it within a bony basket." In some cases the fossa was completely roofed over and the anterior and posterior clinoidal processes have even overlapped, and

an increased density of bone in the roof of the orbits and sphenoidal and ethmoidal sinuses was also noticed in a large proportion of these cases. Other cranial bone lesions have been associated with hypopituitarism, such as hydrocephalus, fracture, syphilitic ostitis, Paget's disease, etc. The effect of these in producing hypopituitarism is probably that of increasing intracranial tension causing pressure, atrophy and hypofunction of the gland.

The character of the sella turcica in its relation to salient features of symptomatology is embraced in the following tabulation by Timme(*b*).

Character of Sella Turcica	*Salient Features of Symptomatology*
Group "A"—With no demonstrable physical enlargement or diminution. Seemingly normal sella.	*Underactivity.* — Usually undersized; maxillary prognathism; crowded teeth; adiposity; Fröhlich's dystrophy; low blood pressure; menstrual disturbances; diminished libido; diabetes insipidus. Somnolence; mentally dull and apathetic; lack of concentration. High sugar tolerance. *Overactivity.*—Frequent and severe headaches; rapid growth; moderate contraction of visual fields; sexual trends; high blood pressure. Great mental activity; initiative; irritability. Low sugar tolerance.
Group "B"—With demonstrable smallness of sella turcica and lack of cavity space for proper expansion of the gland.	Signs of congenital hypopituitarism; with or without headaches; Fröhlich's dystrophia adiposogenitalis; lack of proportionate skeletal build; fatigability; adiposity; usually small genitalia and perhaps reversion in type; sex abnormalities. *Mental Signs.*—Compulsions; lack of inhibition; pathological liars; intellectual and moral inferiority; little initiative; epilepsy. High sugar tolerance. Frequent relative lymphocytosis.

Character of Sella Turcica	*Salient Features of Symptomatology*
Group "C"—Demonstrable original smallness of sella turcica with erosions, enlarging the cavity in any or all directions.	*Pressure Signs.* — Long-continued and periodic headaches, occasionally migrainous with ophthalmoplegia—third nerve, fourth nerve, sixth nerve; unilateral temporal headache with lacrimation (nerve from ophthalmic division of fifth); epilepsy with later uncinate fits. *Metabolic Signs.*—Fatigability with headache and irregular menses and suprarenal deficiency. Secondary frequently to status thymico-lymphaticus. Disturbances in growth; acromegaly; spacing of teeth; prognathism. *Mental.*—Slow development; gradual self-adjustment; and cure. IF EROSION ANTERIOR.—Bitemporal hemianopia. IF EROSION POSTERIOR.—Pyramidal-tract lesions. IF EROSION LATERAL.—Oculomotor disturbances; migraine.
Group "D" — Demonstrable enlargement in all cavity dimensions.	*Pressure Signs.*—Headache; bitemporal hemianopsia; oculomotor palsies; epilepsy; intracranial pressure; papilledema. *Metabolic Signs.*—ACROMEGALY; gigantism; disturbed sugar tolerance; etc.

Skeletal Undergrowth and Infantilism

One of the important functions of the pituitary gland is to stimulate connective tissue growth, especially that of bone. Hypophyseal insufficiency, therefore, leads to undergrowth and defective skeletal development. If the condition begins very early in life or is possibly congenital in origin, hypophyseal dwarfism or infantilism results corresponding to cretinism, which is the result of thyroid insufficiency in early life.

If the process begins later during the growing period, the stature is somewhat diminished in size but usually not sufficient to be classed as dwarf. However, growth may suddenly become arrested at any age when the infantile characteristics will be retained throughout life.

In the adult form of dystrophia adiposogenitalis in which the symptoms date from the period of adolescence other changes than the mere failure of long bones to develop occur, especially in the male in which

Fig. 7. Delayed epiphyseal union and tapering of the fingers. (Case of Ebaugh and Hoskins.)

the skeletal structure is built on feminine lines, to which reference has previously been made.

The most significant of these are the broad pelvis, genu valgum and long hands with tapering fingers. X-ray of the terminal phalanges generally shows persistent epiphyseal lines. In large hypophyseal strumas associated with hypopituitarism the upper maxilla may become prominent. This condition has been designated maxillary prognathism in contradistinction to mandibular prognathism characteristic of acromegaly (Cushing(*b*)). The head is often small, the distance between the eyes narrowed and the teeth broad and malformed.

Other glands besides the pituitary and thyroid in which underdevelopment and infantilism have been observed, both clinically and experimentally, are the gonads, adrenals, thymus and pancreas. Many of the doubtful clinical cases are really of pituitary origin. Numerous cases obscure in origin have recently appeared in the literature in which autopsies showed gross pituitary lesions. Included in these reports are cases of the "Lorain"—(Levi, Rennie, Cushing)—of the "Brissaud"—(Leman, van Wart, Hewlett(*a*)—and of the "Paltauf"—(Kraus)—types. There is a group of preadolescent cases of hypopituitarism with skeletal overgrowth, adiposity and hypogenitalism. The condition has been described by Neurath, who considers the basis for the syndrome a primary lesion of the gonads, and also by Cushing(*b*) who interprets the phenomenon as being due to heteroactivity of the pituitary gland with excessive anterior lobe secretion and diminished posterior lobe secretion.

Fig. 8. Case of dystrophia adiposogenitalis in a girl. (Personal observation.)

A distinguishing feature between infantilism of the eunuchoid type (primary genital dystrophy) and the pituitary type (dystrophia adiposogenitalis) is that in the former the epiphyseal closures of the long bones are delayed much longer—sometimes throughout life—than in the hypopituitary state. This permits the extremities to grow in length, out of proportion to the rest of the body. Falta(*c*) suggested a simple method of differentiation between the two types based on these facts; namely, the distance from the symphysis to the heel is greater than from the symphysis to the top of the head in primary genital dystrophy; whereas in primary dystrophia adiposogenitalis the upper measurements exceed the lower.

Simmonds(*m*) considers that the same process in the anterior lobe of the pituitary which causes cachexia in the adult causes infantilism in early life. He reports a case with autopsy findings, which shows the character of the pituitary lesion and its effect on other glands of internal secretion and development of the genitalia. The case was a man 21 years old and 3½ feet tall. He was beardless and had no axillary or pubic hair. External genitalia were infantile in size. The testicles were the size of peas, weighing respectively 0.9 gram and 1.2 grams. The

prostate and seminal vesicles were the size of those of a nursing infant. The thyroid weighed 2.0 grams; the thymus, which contained a large amount of fat weighed 2.5 grams, and the adrenals weighed 2.0 grams. There were no histological changes found in the thyroid, adrenals, pancreas, liver and spleen. The pituitary was very small weighing 0.2 gram. Macroscopically the gland showed the posterior lobe normal and intact; the anterior lobe was completely atrophied.

Genital Hypoplasia

Faulty development of the genitalia and of the secondary sexual characters occur in typical cases of dystrophia adiposogenitalis. In the male the penis is rudimentary and it may be almost completely buried in cushions of fat. Cryptorchidism with absence of spermatogenesis frequently occurs; one or both testicles may either be partially or entirely unde-

Fig. 9. Genital hypoplasia in case of dystrophia adiposogenitalis. (After Falta.)

scended. They are diminutive in size. The scrotum and prostate also remain abnormally small. In the female the external genitalia as well as the reproductive organs remain infantile. The clitoris is short and underdeveloped and the labia minora are small. The uterus retains its infantile shape and size, and the ovaries may not be palpable. Although the breasts appear large and normally developed, they are deficient in glandular structure and the nipples are small and retracted. The size of the breast is mainly due to an increased accumulation of fatty tissue. As

a rule both menstruation and ovulation are absent, as well as other signs which characterize the development of puberty; namely, a scantiness or absence of axillary and pubic hair, change of voice, etc. In the reversion of sex type in the male there is often a well marked feminine distribution of hair, especially the pubic hair; the face usually remains beardless.

If the disease first manifests itself after puberty, retrogressive changes occur, which result in genital hypoplasia; impotence occurs in men and menstruation ceases in women. There is also loss of libido in both sexes.

Polyuria

Diabetes Insipidus.—In cases of dystrophia adiposogenitalis elimination of urine is frequently increased. This may vary from a slight or moderate increase over the normal (polyuria) to an enormous quantity reaching as high as 13000-15000 c.c. per diem (diabetes insipidus). The latter was formerly attributed to posterior lobe deficiency (Cushing(*b*)) but more recent investigations (Houssay and Leschke) failed to corroborate this view. Houssay established experimentally a cerebral basal zone within which pricking generated polyuria. This zone is limited in front by the optic chiasm and behind by the peduncle protuberance. Leschke pointed out the fact that while lesions of the hypophysis, such as trauma, sarcoma, metastatic carcinoma, tuberculosis, syphilis, etc., have been demonstrated in diabetes insipidus, similar lesions in the midbrain, especially those involving the tuber cinereum, may produce diabetes insipidus with the hypophysis intact. Removal of the gland does not produce polyuria, whereas a piqûre in the tuber cinereum does produce it. He regards the hypophysis as incidental, and, if associated with diabetes insipidus, that the latter condition is due to pressure on or extension of the lesion into the tuber cinereum.

Veil produced experimental diabetes insipidus which he divided into two classes, according to NaCl concentration. He states that a piqûre in the fourth ventricle produces polyuria with an increase of the NaCl in the urine (hyperchloruria) and a piqûre in the midbrain produces polyuria, with a decrease of NaCl in the urine (hypochloruria).

Diabetes insipidus has occurred in individuals with extensive cranial bone lesions. A case reported by Schüller(*c*) was associated with definite alterations in the sella and one by Christian, in which very slight sellar changes were observed.

A personal observation (Group A, case xv), with a positive Wassermann and marked thickening of the cranial bones, especially the occipital, and a shallow closed-in sella, due to enlargement and encroachment of the

clinoid processes, presented marked symptoms of diabetes insipidus and adiposogenital dystrophy.

The unique case reported by Marañon and Rosique is of great clinical interest. A boy, who received an accidental bullet wound in the mid-frontal region, showed no nervous or mental symptoms, but later developed all the signs of Fröhlich's syndrome together with severe diabetes insipidus. An attempt to remove the bullet proved fatal. At post-mortem the bullet was found in the region of the infundibulum, the stalk of the pituitary body being interrupted by the cicatricial tissue formed around the bullet. The pituitary itself was quite unharmed. The authors maintain that the occurrence of diabetes insipidus was the result of blocking of the canal in the stalk of the infundibulum.

Cachexia Hypophysopriva

During the earlier experimental studies of the pituitary it was observed (Vassale and Sacchi: Paulesco(*b*)) that a peculiar train of symptoms followed within a few days after the complete removal of the gland in animals. Among the symptoms enumerated were tremors, fibrillary twitchings, arching of the back, insensitiveness, diminution in pulse and respiratory rate, fall in temperature, apathy, coma and death. These acute symptoms and death do not occur if a small viable portion of the anterior lobe is allowed to remain (Paulesco(*b*)). The immediate transplantation of the removed gland, or subcutaneous injection or feeding of anterior lobe will also prevent a threatened cachexia hypophysopriva (Cushing, et al.). The condition has been observed clinically—autopsies showing either a complete destruction of the gland or of the entire anterior lobe (Simmonds (*m*), Fraenkl (*b*)).

Adenoids and Pituitary Deficiency

A relation between adenoid growth and hypopituitary states has been suggested, and cases have been cited of hypophyseal feminism, the cause of which was attributed to adenoids. This view is based on the discovery by Erdheim(*b*) (1904) of a small epithelial body situated behind the alae of the vomer, which has been designated "Hypophysis pharangea." It is a part of the hypophyseal system, representing the lowermost extremity of Rathke's pouch and resembles in its histological structure the glandular lobe of the pituitary.

Bryant considers that chronic nasopharyngeal infections interfere with pharyngeal pituitary function, and that the removal of tonsils or adenoids, which tend to relieve the chronic infection, result in more rapid growth and improved nutrition. Leegaard reported a case of retropharyngeal tumor of hypophyseal structure.

Citelli and Caliceti reported three cases of hypophyseal feminism in soldiers, who had suffered from adenoids. The skeleton and genitalia were normal, but they showed a condition of hypotrichosis, delicate skin, development of the mammae, feminine distribution of the pubic hair and sexual frigidity.

Multiple Hemangiomas.—Multiple hemangiomas of the skin were observed in two cases of dyspituitarism by Head. In one case the skin of the scrotum, thighs, back and abdomen was affected, in the other the scrotum and the mucous membranes of the lips and mouth were involved. Hemangiomas were present in two of the writer's series, both typical cases of dystrophia adiposogenitalis. In the one they appeared on the chest, back of the neck and arms, in the other on the mucous membrane of the upper lip.

Illustrative Cases

Illustrative Case I.—The following case, studied by Ebaugh and Hoskins, presented many of the characteristic features of the masculine type of dystrophia adiposogenitalis. (Fig. 10.) The patient was

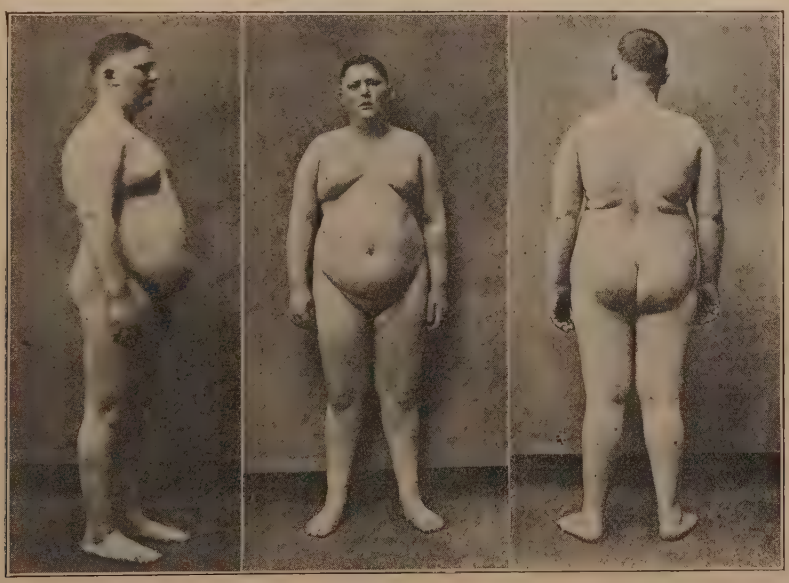


Fig. 10. Dystrophia adiposogenitalis—typus femininus—age 16 years. Note the obesity, genu valgum, large breasts, large mons, rudimentary genitalia, etc. (Courtesy of Ebaugh & Hoskins.)

sixteen years of age and complained chiefly of obesity, lack of development of the genital organs, and a tired feeling in the afternoon.

At birth he was small and puny, but growth and development was apparently normal until he attained the age of ten, when he began to

take on fat. Although he progressed satisfactorily in his studies at school, yet at twenty-one his general demeanor was infantile; point scale estimate of mental capacity was that of ten and a half years, and his intelligence coefficient was .77. He lacked initiative and emotional poise; cried daily; was quarrelsome, irritable and stubborn, and lied to his employer. Since the onset of his symptoms he had been unduly sensitive, and at times over-affectionate.

The patient was 5 feet 1½ inches in height and weighed 162 lbs., having gained 40 lbs. in three years. He presented a striking appearance with special reference to distribution of fat and rudimentary condition of the genitals. The deposits of fat were especially marked in the mammae, which were large and pendulous. He had a marked protruding and overhanging abdomen, a large pad of fat just above the symphysis pubis and across the buttocks. The thighs were huge, graceful and tapering. The pelvis was broad and suggested that of the feminine type. He exhibited genu valgum, and there was a slight degree of lumbar lordosis present.

Fig. 11. Showing irregularity and separation of teeth. (Case of Ebaugh and Hoskins.)

The circumference at the plane of the nipple was 96 cm.; at the umbilicus 106 cm., and at the trochanters 102 cm.

The shape of the skull suggested acromegaly, the lower half of the face being more prominent than the upper. There was a tendency to malar prominence.

The genital organs were underdeveloped and suggested that of a boy ten years younger. The penis was rudimentary. The scrotum was small and buried in fat. Both testicles were undescended and could only be palpated with difficulty at the external abdominal rings. There was no history of auto-eroticism or of any homo- or heterosexual trends. Crines pubis were extremely scant and hirci almost entirely absent.

The hands and feet were small and the nails ridged, brittle and cracked readily. There was no abnormality of the visual fields. The blood pressure and pulse rate were normal. The X-ray showed a normal sella, prognathism with separation of the teeth and delayed epiphyseal closure of the phalangeal bones.

The urine was negative. The blood showed a red cell count of 4,126,000, hemoglobin 75 per cent, white count 8,960, and a differential count as follows: polymorphonuclear 64 per cent, basophiles 0.5 per cent, eosino-

philes 1 per cent, lymphocytes 26.5 per cent, large mononuclears 5 per cent, transitionals 3 per cent.

Treatment consisted at first of pituitary (whole gland) followed by a combination of pituitary and thyroid to which subsequently was added suprarenal gland. Despite thyroid medication basal metabolism was 4 per cent below normal. The patient improved on all of the above plans of treatment. He became less infantile in his habits; condition of hair and fat dystrophy improved; testicles descended and genitalia showed signs of development.

Fig. 12. GROUP A, CASE XV, showing fat dystrophy at end of 2 months from the time she began to increase in weight. Note the size and shape of the upper thighs, gluteals and abdomen.

Illustrative Case II (Fig. 12).—The following case presents the typical syndrome of dystrophia adiposogenitalis in the female: The patient, twenty-four years of age, was employed as a cashier. Except for a sister, who was suffering from goiter, her family history was negative. As a child she had scarlet fever and measles, and later occasional sick-headaches; otherwise her general health had been good, and her development both mental and physical normal. The onset of her symptoms dated to an attack of grippe from which she suffered eighteen months previous to examination. Following this attack menstruation, which had always been regular and normal from the age of fourteen, became scant and after three months ceased entirely. Five months later an intense polyuria developed. Her average weight, which was one hundred and five pounds, remained stationary for thirteen months after cessation of menstruation, then there was a sudden increase due to a rapidly developing obesity, gaining twenty-two pounds in five weeks. In two months, at the time of examination, she had gained twenty-eight pounds and subsequently reached one hundred and forty-nine pounds. The obesity was of the girdle type with broad hips, large, tapering thighs, and excessive accumulation of subcutaneous fat in the lower abdominal wall. In addition she observed a slight increase in the size of her breasts and some local deposits of fat over her shoulders. There was no increase in the size of the face, neck, forearms and hands, legs and feet.

The skin was dry, thin and peculiarly delicate, white and transparent (alabaster skin). The fingers were tapering, and the hair, with the exception of some scantiness of the eyebrows, was normal in character and distribution.

She had an insatiable thirst, getting up four or five times every night, voiding enormous quantities of clear, limpid urine and drinking three glasses of water each time before returning to bed.

She also complained of dyspnea on exertion, excessive fatigue, neuromuscular pains, drowsiness, mental irritability, emotional disturbances, and headaches. Despite the fact that she rapidly gained in weight her appetite was poor and her bowels were constipated. Gastric analysis showed free HCl 46 and total acidity 76. The blood showed a moderate grade of anemia and a positive Wassermann reaction. She eliminated from 8000 to 13000 c.c. of urine in twenty-four hours. The specific gravity ranged from 1.002 to 1.004 and was negative both chemically and microscopically. The pulse was slow and blood pressure subnormal, systolic 104, diastolic 84. There was a soft, blowing systolic murmur at the apex. Slight pitting occurred on pressure over the shins. Temperature was subnormal. The thyroid, which contained a small, firm, nodular mass, was slightly prominent. Tendon reflexes were sluggish. There were no visual field disturbances and the eyegrounds were normal.

Fig. 13. Abnormally small closed-in sella: Enlargement of the anterior clinoid processes and thickening of the cranial bones.

GROUP A, CASE XV. Dystrophia adiposogenitalis; amenorrhea, diabetes insipidus, positive Wassermann, narcoleptic attacks, hypotension. (Röntgenogram by Dr. A. Cotton.)

X-ray findings. The interpretation of a lateral plate showed bones of the cranial vault unusually thick, especially those of the posterior portion. The sella was small and flattened and the anterior clinoid processes much thickened and elongated. (Fig. 13.)

There was no amelioration of symptoms on antiluetic treatment. On thyroid and pituitary gland substance the fat was temporarily redistributed and the diabetes insipidus was partly controlled by pituitrin. (Fig. 14.)

The case was lost sight of for two years when she was again seen in consultation with Dr. Hocking the day before she died. With the exception of two months, she was regularly employed until six weeks before death, when she was compelled to discontinue her work on account of lethargy, stupor, and dullness. For several months previous she had

been drowsy and stuporous, and unless aroused, slept all day without taking a morsel of food—at one time sleeping almost continuously for two weeks. Her memory was extremely poor, and she had lost all initiative. There was no return of menstruation. Vision continued normal. She had persistent headaches and frequently vomited. Polydipsia and polyuria gradually subsided and during the preceding two months she voided a normal amount of urine. Pulse had become more rapid and the blood pressure had fallen to systolic 80 and diastolic 60 (Dr. Hocking).

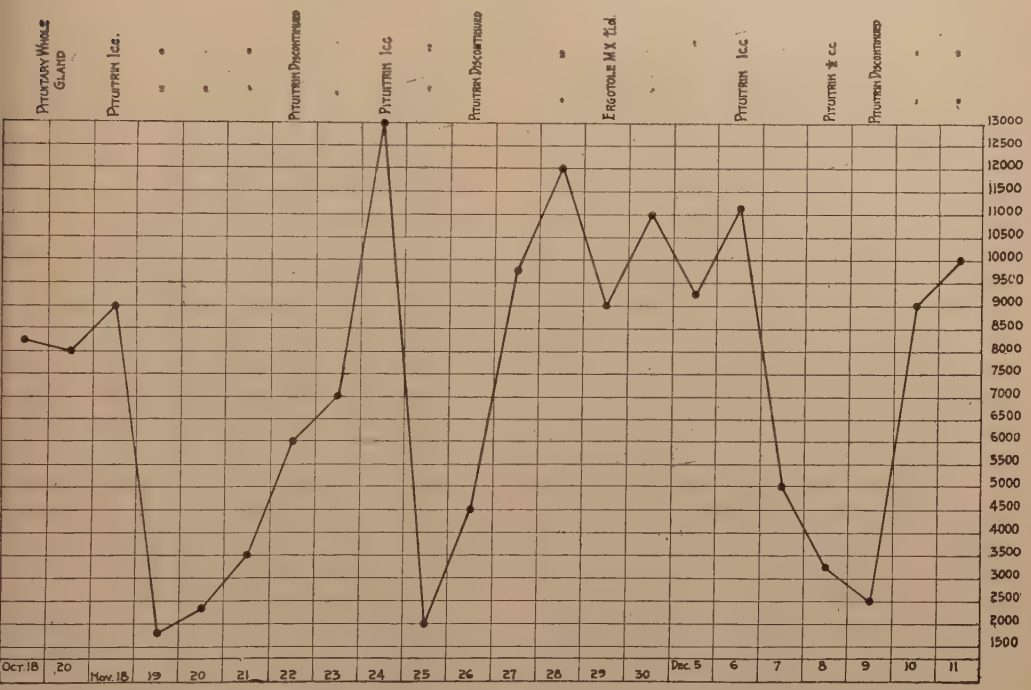


Fig. 14. Chart showing effect of pituitrin on the excretion of urine in diabetes insipidus. GROUP A, CASE XV.

Examination showed the patient in a state of narcolepsy from which she could be only temporarily aroused. She had a slight rise in temperature, due to an infection of her throat. Her pulse was rapid, 120 beats to the minute, and her respiration was 40. The obesity had increased, but the character and distribution of fat remained unchanged. There was an absence of hirci and crines pubis. The color and texture of the skin presented the same characteristic appearance observed at the beginning of her illness. There was drooping of the upper eyelids, more marked in the left than the right. Pupils responded sluggishly. Hippus was present in both eyes. The patient passed into profound coma and died the next day.

Illustrative Case III (Fig. 15).—The following is an example of pituitary dwarfism with dystrophia adiposogenitalis in a boy aged 17 years, seen in consultation with Dr. Gillis and Dr. Krause. His father is living and well, of medium height and weighing 148 pounds. His mother had died eleven years before from a tumor at the base of the brain. She had suffered for seven years with headache previous to her death, and was sick at the time of the birth of the patient. There is one brother living and well, 20 years old, normally developed both mentally and physically and five feet, nine inches tall. One sister died in infancy.

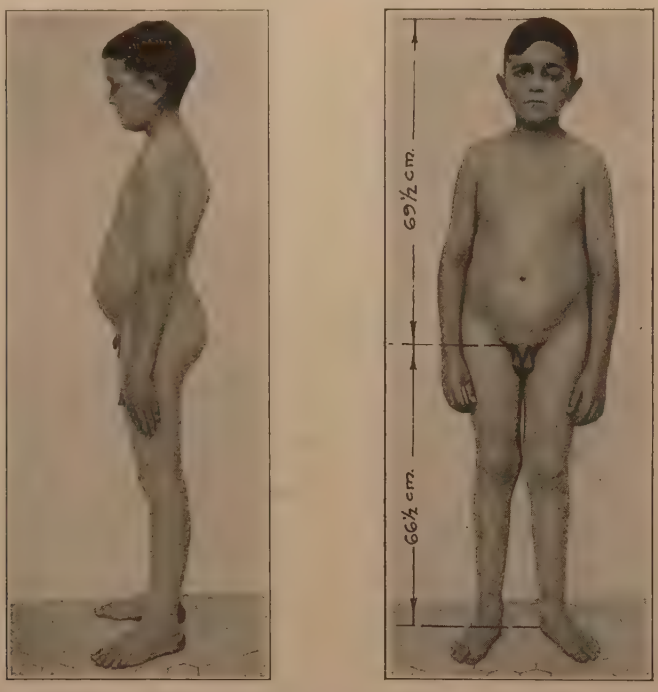


Fig. 15. Dystrophia adiposogenitalis in a boy seventeen years of age. Note the feminine characteristics; well developed breasts, large mons, broad hips and genu valgum, also the genital hypoplasia, absence of crines pubis and shortness of the lower extremities.

The patient was normal at birth and remained so until he was 13 years of age when he ceased to grow. He entered school at the age of six and a half years, and progressed favorably in his studies until he completed the seventh grade, when he discontinued school on account of drooping of the left eyelid. In his play he showed a special fondness for baseball and the usual outdoor games, and always selected boys of his own age for playmates. He had no sexual awakening; no erections and no erotism. His demeanor was that of a child well disciplined, and he had a cheerful

disposition. His strength was good, and he was accustomed to manual labor, hauling lumber with ox-team. There were no symptoms referable to his gastro-intestinal, cardiovascular, respiratory or genito-urinary systems, and no neuromuscular symptoms except ptosis of (left) eyelid and strabismus.

Physical Examination.—Patient looked bright and answered simple questions promptly and intelligently. His appearance was that of a boy of thirteen, or four years his junior both in regard to height and general development. The general outline of the body was distinctly feminine with delicate features, especially the texture of the skin and the size and shape of the extremities. His breasts were well developed. The lower abdomen was quite prominent and the hips and upper thighs were relatively large. The skin was peculiarly dry, light in color, and delicate for a boy much exposed to the sun. There was complete absence of body-

Fig. 16. Left—Pituitary hands—"Type en petite" of the boy (aged seventeen) seen in Figure 15. Note the gracile form, the smooth delicate skin and the tapering fingers as compared to those of a normally developed boy nine months younger.

hair. The face was beardless; on the upper lip there were a few fine lanugo hairs and the axillary and pubic hair were absent.

There was a slight prominence over the occipital bone, otherwise the outline and contour of the skull was normal. Directly in front of the right ear was a small congenital nipple-like projection, the size of a pea. The facies suggested adenoids. The upper teeth projected beyond the lower, producing well marked maxillary prognathism. The left eyelid was ptosed. The left pupil was larger than the right but responded well to light and accommodation. External strabismus was present in the left eye. Mucous membranes were pale. The upper teeth were irregular; the lower were small, separated, and showed evidence of pyorrhea. No history could be obtained in regard to the time of dentition. The super-

ficial lymph glands were slightly enlarged. He exhibited the characteristic pituitary hand (type en petite) with delicate tapering fingers and absence of the crescents in nearly all of the nails. (Fig. 16.) There was marked vasomotor congestion of both hands. The genital organs were infantile in character; both testicles were descended and about the size of an olive. The scrotum was normally developed and the mons was very large. The penis was rudimentary, measuring 3 cm. in length, and was partially buried in a cushion of fat formed by the enlarged mons. The lower extremities were relatively short. Genu valgum and pes planus were marked. Tendon reflexes were normal.

Fig. 17. Closed-in sella of case illustrated in Figure 15. (Radiogram by Dr. Cotton.)

Ophthalmic Examination.—R. vision 20/30. L. vision 20/70 due to squint. Left eye showed almost complete paralysis of the third nerve; ptosis, partially dilated pupil. No movements up, down, in, from beyond the midline. Eyegrounds were normal. Fields showed slight contraction for white; the fields for red were normal. (Dr. Downey.)

Laboratory Findings.—Röntgenograms exhibited malformed and closed-in sella turcica, some atrophy of the bones of the hand and forearm with widening of the epiphyseal lines (Figs. 17, 18.) Repeated urinary examinations were negative. Examination of the blood showed: hemoglobin 85, erythrocytes 4,600,000, leukocytes 5,860, differential count—neutrophiles 76, small mononuclears 19, large mononuclears 4,

eosinophiles 1; Blood Wassermann negative; Blood Sugar 0.17; Sugar tolerance positive after administration of 100 gm. of dextrose.

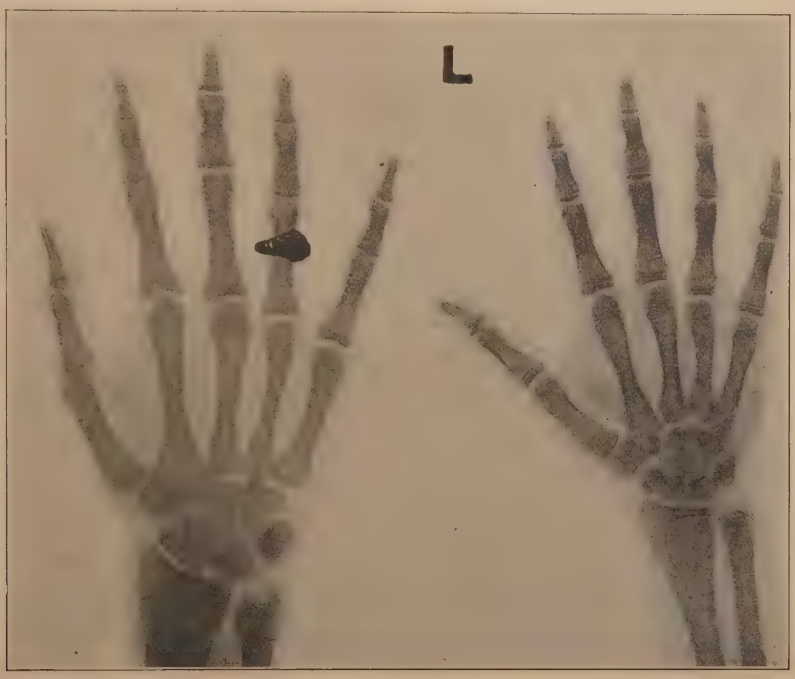


Fig. 18. Showing the comparison between the epiphyseal lines of the normal and pituitary hand, illustrated in Figure 15. (Radiogram by Dr. Cotton.)

Chronological arrangement of important contributions to literature on the pituitary gland, prior to Fröhlich's description of the syndrome now known as dystrophia adiposogenitalis.

2nd Century—Galen—Thought nasal secretions originated in the pituitary body.
(Garrison's Hist. Med. p. 200)

1543 Vesalius, A.—Upheld Galen's idea.
(Fabrica, lib. VII, Cap. XII)

1660-62 Schneider, C. V.—Overthrew Galen's idea and stated that nasal secretions do not originate in the pituitary body.
(De catarrhis, Wittenberg, 1660-62)

1672 Lower, R.—Supported Schneider's view.
(Dissertatio de origine catarrhi in qua ostenditur illum non provenire a cerebro, in his Tractatus de corde, London, edition of 1680, 163, 175)

1682 Willis, T.—Observed abnormalities in the size of the pituitary. "Betrachtete den Hirnanhang als Reinigungsorgan des Hirnes"—Frankl-Hochwart.

(Die Diagnostik der Hypophysistumoren ohne Akromegalie—L. v. Frankl-Hochwart, Wien. Wchnschr. 1909, 59, 2127)

1700 Bonetus, T.—Reported a case of hypophyseal tumor.
(Anatomia Practica, Genevae, 1700)

1705 Vieussens, R.—Reported a case of tumor of the hypophysis with amaurosis and epileptiform movements.
(For original data see his: Novum vasorum corporis humani systema. Amstelodami 1705, 12°. 248 et seq.)

1718 Petit.—Found the gland "squirrheuse" in subjects with hydrocephalus.
(Mémoires de l'Academie royale des Sciences, année 1718, 99)

1724 Wepfer, J. J.—Gave a description of anatomical abnormalities of the pituitary.
(Historiae apoplecticorum, etc. Amstelaedami, apud Janssonio-Waesbergios 1724)

1769 DeHaen, A.—Mentioned amenorrhea in connection with hypophyseal tumor.
(Extrait d'une observation rapportée. Ratio medendi, tom. 6, cap. 6, de cranii ustione, 271)

1779 Morgagni, G. B.—Mentions a light-yellow tint of the gland which occurs under certain circumstances.
(De Sedibus et causis morborum, per anatomen indagatis. Praefatus est S.A.D. Tissat M.D 4°. Ebroduni in Helvetia 1779)

1781 Greding, C. G.—Noted changes of the hypophysis in epilepsy.
(Insunt quaedam de primis variolarum initiis, earum que contagione admodum virulenta. Ad Carolum Gottlob Kuehnium episto 16 pp. 4°. Lipsiae ex off. Saalbachia 1781)

1810 Wenzel, J.—Attributed epilepsy to changes in the pituitary, which gland he considered most important. He also referred to the enlargement of the sella turcica.
(Cited by Frankl-Hochwart, Wien. Wchnschr. 1909, 59, 2127)

1811 Wenzel, J.—Found the infundibulum reddened and inflamed in an epileptic.
(Observations sur le cervelet et sur les diverses parties du cerveau dans les epileptiques; 8°. 1811; trad. de Breton, p. 216)

1823 Rayer, P.—Published a collection of cases of hypophyseal disorder prior to 1823.
(Archives gén. de Médecine, 1823, 3, 350-367)

1823 Ward, J.—Reported a case of amaurosis produced by enlargement of the pituitary.
(London Medical Repository, N° Sept. 1823, 20, 217)

1833 Hedlund.—Reported a case of hypertrophy of the pituitary with blindness.

(Hypertrophie af glandula pituitaria och deraf beroende blindhet. Ars-Beratt. on Svens. Lak.-Sallsk. Arb. Stockholm, 1833, pp. 20-23)

1840 Mohr, B.—Described a case of hypophyseal tumor with obesity, visual disturbance, headaches, vertigo, clumsy movements and mental symptoms.
(Hypertrophie der Hypophysis cerebri und dadurch bedingter Druck auf die Hirngrundfläche, insbesondere auf die Sehnerven, das Chiasma derselben und den linkseitigen Hirnschenkel. Wchnschr. f. d. ges. Heilkunde (Berl.), 1840, 6, 565-571)

1855 Harvey, J. R.—Described a sudden and complete amaurosis result of pituitary abscess and a scrofulous tumor.
(Dublin, Q.J.M.Sc., 1855, XX, 220-222)

1866 Leber, Th.—Quoted a case of optic neuritis and bilateral abducent paralysis with gliosarcoma of the infundibulum and tuber cinereum.
(Gliosarkom des Infundibulum und Tuber cinereum. Neuritis optica, Beiderseitige Abducenslähmung. v. Graefe's Arch. f. Ophth. XIV, 2, 333-378)

1886 Marie, P.—Described the syndrome of acromegaly.
(Sur deux cas d'acromégalie; hypertrophie singulière non congénitale des extrémités supérieures et inférieures céphalique. Rev. de méd. 1886, vi, 297-333)

1887 Story, J. B., Nettleship, E., Griffith, H., Anderson, J., Coupland discussed pituitary lesions in relation to eye symptoms, obesity, menstrual disturbances and mental manifestations in a meeting of the Ophthalmological Society of the United Kingdom. (Brit. Med. J., 1887, i, 1334)

1889 Rogowitsch, N.—Noted hypertrophy of the pituitary after removal of the thyroid.
(Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse. Beitr. z. path. Anat. u. z. allg. Path., 1889, iv, 453-469)

1890 New Trend—Study of the anatomical side.
(Frankl-Hochwart—Wien. med. Wchnschr. 1909, 59, 2127—)

1895 Oliver, G. & Schäfer, E. A.—Discovered that the pituitary was a gland of internal secretion.
(On the physiological action of extracts of pituitary body. J. Physiol., 1895, 18, 276-279)

1898 Comte, L.—Observed that the anterior lobe enlarges during pregnancy. (Confirmed by Erdheim and Stumme in 1909)
(Ziegler's Beitr. z. pathol. Anat. u. z. Allg. Pathol. 1898, 23, 90)

1899 Oppenheim, H.—Confirmed the enlargement of the sella turcica by means of the X-ray
(Cited by Frankl-Hochwart, Wiener med. Wchnschr., 1909, 59, 2127—)

1901 Fröhlich, A.—(Study of the clinical side.) Description of syndrome: obesity, general hypoplasia, infantile genitalia, etc., with pituitary tumor.
(Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie. Wien. klin. Rundschau, 1901, XV, 883-906)

Symptomatology

The signs and symptoms associated with hypophyseal dystrophia adiposogenitalis are essentially those of hypopituitarism. The syndrome as described by Fröhlich(*a*) is not a clinical entity but a mere grouping of the most characteristic symptoms in selected cases of hypophyseal tumor (Lyon); and the most modern conception based largely on the knowledge obtained through physiological investigation includes all those symptoms which are the direct result of underfunction.

Fig. 19. Von Fröhlich's case of hypophyseal obesity after operation. (After A. Biedl, "Innere Sekretion," published by Urban & Schwarzenberg, Berlin.)

In order to present the subject in a thorough and comprehensive manner it seems advisable first to give a general description of the symptoms and then to consider more in detail the special features and allied conditions.

General Description.—The two striking symptoms emphasized by Fröhlich in his original report are obesity and genital hypoplasia. These symptoms naturally vary somewhat, depending upon the sex and the age of the individual at which the disease first manifests itself. The obesity may be enormous. The fat usually assumes a fairly definite type of distribution with relative increase of subcutaneous deposits about the hips, thighs, mons and lower abdomen—girdle obesity. In early life, and occasionally in adults, the adiposus is more general, involving the mammae, pectorals, clavicular spaces, etc.

There are also certain characteristic integumental changes. The texture of the skin is remarkably delicate, and the fair complexion —"peaches and cream" variety characteristic of youth may persist long after adolescence. In the severe forms it may be white and transparent like alabaster. To the touch it feels cool and dry, and sometimes it exfoliates; in rare instances it may resemble that in myxedema or in scleroderma. The

fingers taper; the nutrition of the nails is normal, although the crescents at the base are often absent. There is also a marked change in the character and distribution of the hair with a tendency to hypotrichosis. The axillary hair (hirci) and the pubic hair (crines pubis) are scant or absent, if the symptoms of the disease antedate puberty. The male may not be able to grow a beard, and the upper outline of the pubic hair assumes the horizontal form, the type met with in the female (typus femininus). In the female, on the contrary, the distribution of hair may approach the masculine type.

Sexual hypoplasia or the genital syndrome is a factor equally as important as obesity in typical dystrophia adiposogenitalis. In the pre-

Fig. 20. The pituitary hand. Note the gracile, tapering fingers.

adolescent male the genitalia are rudimentary, including the penis, scrotum and testicles; the latter are usually partially descended or entirely undescended (criptorchidism). The secondary sex characters frequently do not appear. This condition is generally associated with feminine characteristics, especialy in regard to the distribution of the hair and deposits of fat above referred to, in addition to occasional enlargement of the breast and juvenile voice. Other signs of feminism are the skeletal features; namely, gracile extremities, small hands and feet, tapering fingers, round limbs, genu valgum and broad pelvis. In the adult male, whose genitalia had been normally developed, the disease causes retrogressive changes resulting in genital atrophy with impotence, absence of libido and tendencies to feminism.

In the female sexual infantilism occurs with hypoplasia of both external and internal genitalia with symptoms of frigidity, amenorrhea and sterility. In conjunction with sexual infantilism and adiposity in young individuals, dwarfism frequently occurs, due to skeletal undergrowth. Falta(*c*) quotes cases in which growth was arrested at five (Goldstein),

seven (Neurath), ten (Bournier), and among others cites his own cases in which growth ceased at eight and thirteen years of age respectively.

Nervous and Mental Manifestations.—Headache is one of the most constant symptoms of pituitary disease. It is usually severe and intractable, occurring in paroxysms and described as being located between the temples or deep behind the eyeballs. It is frequently associated with other symptoms of intracranial pressure, such as vertigo, projectile vomiting, and visual defects due to optic nerve lesions, such as optic atrophy and choked disc. Hypophyseal tumors may cause local pressure upon the optic chiasm and produce well marked eye symptoms of which bitemporal hemianopsia is the most important. Homonymous hemianopsia also occurs. A tumor which extends beyond the margin of the sella may involve the third cranial nerve, producing external strabismus, or the sixth cranial nerve producing internal strabismus.

The so-called uncinate attack (epileptiform seizures with gustatory and olfactory aura) result from pressure on the uncinate gyrus. In the early and milder forms of dystrophia adiposogenitalis mental symptoms are not marked. In more advanced cases they may vary from a mild psychosis to states of insanity. Drowsiness, stupor, and apathy are common symptoms. Patients are often languid, irritable, and lack self-control. Neuromuscular pains, such as lumbago and sciatica, were observed frequently in my series. There is diminished excitability of the vegetative nervous system.

The sella turcica is usually enlarged and deformed, if the lesion is due to a tumor, and small and closed-in by the clinoid processes, if the lesion is not due to a tumor. The former is usually associated with neighborhood signs and symptoms. In the latter they are generally absent. This subject in addition to others of equal importance will be considered more fully elsewhere.

Polydypsia and Polyuria are present in many of the cases. The polyuria may be transitory or more or less permanent. When associated with tumors in the neighborhood of the hypophysis, especially those involving the chiasm and subthalamic region or with basilar syphilitic meningitis, a true diabetes insipidus may develop.

Vesical irritability is a common complaint, a symptom which has been ascribed to weakness of the bladder musculature. Albuminuria has not been observed in a single case in the writer's series. In the case reports, as found in literature, reference is rarely made to the presence of albumin in the urine. Sugar, however, does appear in the urine occasionally in hypophyseal dystrophy. Seven cases presenting the picture of diabetes mellitus are found in von Frankl-Hochwart's statistics. It is possible that the few reported cases are mere coincidences of pancreatic diabetes. If they are of hypophyseal origin, they can only be explained on the basis of a functional heteroactivity of the gland: hyperactivity of the posterior

lobe and hypoactivity of the anterior lobe. Such a condition might possibly occur during the transitional stage of hyperpituitarism into a secondary hypopituitarism or a state of dyspituitarism. The chief *gastrointestinal symptoms* are vomiting, projectile in character due to intracranial pressure, and constipation due probably to lack of stimulation of the involuntary muscular fibers of the intestines from posterior lobe deficiency.

Metabolism.—The carbohydrate tolerance is increased in dystrophia adiposogenitalis. This feature, according to Goetsch, Cushing, Jacobson, is due to posterior lobe deficiency and is of considerable diagnostic importance. In some cases the tolerance is almost unlimited, exceeding an amount beyond the capacity of the stomach to take dextrose. It is not unusual to find an assimilation of 300 grams dextrose or more. An actual hypoglycemia may be present. According to Cushing both the increased sugar tolerance and low blood sugar content can be corrected by injection of posterior lobe extract. Other evidence of metabolic disturbances are the diminished carbon dioxid exchange (Benedict & Homans), reduction of oxygen consumption, lowered basal metabolism rate (Plummer), and falling off in the nitrogen balance (Ashner(*a*)). The temperature is subnormal; the pulse and respiration rate are diminished, and the blood pressure is lowered. The temperature anomaly has been attributed to deficiency of the anterior lobe and can be experimentally produced in animals by partial removal of this lobe. Moreover, the injection of anterior lobe extract will temporarily restore the subnormal temperature (Thermic reaction—Cushing). The abnormally low blood pressure, which may fall to 100 or below, is due to lack of the pressor substance, which is a normal constituent of the hypophyseal secretion. Hypotension, therefore, proves to be a common manifestation of hypopituitary states. In exceptional cases with pluriglandular syndromes, in which the low blood pressure is associated with asthenia and pigmentation, a secondary hypoadrenia may be a contributing factor.

The blood presents a fairly constant picture in hypophyseal dystrophy. While there is only a slight reduction of erythrocytes there is an appreciable reduction of hemoglobin. The leucocyte count is usually below the normal. The neutrophilic cells are relatively diminished, whereas the mononuclears, and especially the lymphocytes, are not only relatively but also absolutely increased. Many cases show a tendency to eosinophilia. The mononucleosis and poverty of hemoglobin resemble that of myxedema.

Obesity and General Configuration of the Body

One of the most characteristic symptoms in hypophyseal dystrophia adiposogenitalis is obesity. The question as to what portion of the pituitary gland is concerned in the development of obesity is still a matter of considerable doubt, and various views are held in regard to this matter. Experimentalists generally, however, agree that anterior lobe deficiency is the primary cause. This view is based on the fact that the syndrome of dystrophia adiposogenitalis, with its characteristic obesity, develops after partial removal of the anterior lobe, or after the removal of all of the posterior lobe and a large portion of the anterior lobe; and that, on the contrary, no symptoms develop after the complete removal of the posterior lobe. Cushing and his associates attribute the cause to posterior lobe deficiency, which acts by increasing carbohydrate tolerance with resultant accumulation of fat. (Both views may be in a measure correct, and therefore, it seems for the present at least, best to regard both lobes as factors, the anterior primary and the posterior secondary, which is in accord with the opinion of Schmidt and May who believe that the active principle of the posterior lobe is derived from the Tethelin produced by the anterior lobe.

Fig. 21. Normal female figure and outline. (Copied from A. Thompson's Anatomy for Art Students.)

However, the effect upon the obesity produced by the administration of anterior lobe extract in reducing the fat (Roblee) and in redistributing the fat (Beck(*a*)) suggests hypofunction of the pars anterior.

The obesity may be general, although it is usually characterized by a fairly definite type of distribution in which the deposits of fat are localized chiefly about the hips, the upper thighs, the mons veneris, the lower abdomen, and frequently the mammae. In early life the tendency is toward a more general adiposus, a type illustrated by Fröhlich's case. After puberty there is more variation in form and figure of the body. In a large group of cases, especially in women, there is an enormous preponderance of fat localized in the above mentioned areas in otherwise normally developed individuals. These deposits often appear as huge masses or folds over the buttocks and thighs with an apron of fat (panniculus adiposus) over the lower

abdomen. The predilection for fatty deposits in these areas is one of the most characteristic features of dystrophia adiposogenitalis. Upon careful observation it is found in practically all cases whether the obesity is excessive or slight in degree. Bernhard Mohr (1840) called attention to the increase of fatty tissue in the heart, liver, and mesentery, and Biedl(*c*) observed a remarkable deposition of fat in the omentum and retroperitoneal

Fig. 22. Marked adiposity of the girdle type. Note increase in size of the hips and lower extremities compared with the upper half of body.

space. The fat never appears in the form of lipomas, and as a rule is not tender as it is in Dercum's disease.

In another group the deposits of fat assume a more general distribution, the mammae, shoulders, infra- and supraclavicular areas being involved in addition to those mentioned. Occasionally a collar-like accumulation of fat appears on the neck and a cuff-like deposit on the malleoli. However, the hands and arms, legs and feet generally remain free. This form has been recognized as a familial type and presents a picture of obesity somewhat intermediate between thyroid deficiency and hypophyseal deficiency, and is probably due to hypoplasia of the sex glands secondary to hypopituitarism. Because of the close reciprocal function between the pituitary, thyroid and gonads, true hypophyseal fat-

dystrophies are not very common; on the contrary the mixed or pluriglandular types are quite common. Thus, it is not unusual to find in the same individual clinical evidence of hypothyroidism, hypopituitarism, and hypogonadism in which the form of adiposity varies, according to the relative degree of insufficiency of the respective glands. In a series of one hundred cases of hypothyroidism studied by the writer, 20 per cent showed evidence of hypophyseal fat dystrophy; whereas in a series of forty-six

Fig. 23. Familial type of hypophyseal obesity.

cases of dystrophia adiposogenitalis twenty-seven manifested symptoms of hypothyroidism. Primary genital dystrophy, such as occurs in eunuchoidism, closely resembles hypophyseal dystrophia adiposogentalis in the distribution of fat (von Noorden). However, primary genital dystrophy without an hypophysea syndrome is relatively infrequent. When it does occur it usually becomes early a mixed type in which hypophyseal symptoms predominate.

The source of glandular deficiency can sometimes be ascertained by means of the cosmetic effect produced through localized deposition of fat upon the configuration of the regional parts of the body. Thus the supraclavicular folds are indicative of thyroid deficiency; pads of fat about the

eyeballs, mons and mammary glands suggest gonadal deficiency, while the classical girdle obesity points to hypophyseal deficiency.

All gradations of fat dystrophy ranging from the slightest deviation of normal body configuration to veritable monstrosities may be encountered, the degree depending upon the relative diminution of pituitary function and the secondary disturbances of function in other endocrin glands. In complete loss of function (apituitarism) obesity does not develop, on the contrary there is loss of weight with emaciation and cachexia (cachexia hypophysopriva).

A unilateral dystrophy of fat occurred in several of the writer's cases in connection with hypophyseal dystrophy. This may be suggested by a slight relative increase of size, on the affected side, of the lobule of the ear, and the breast, and perhaps a slight facial asymmetry. It can be more definitely determined by comparing the measurements of the circumference of the arms and legs. This observation confirms that of Neiden's case, cited by Macnab, in which obesity first manifested itself on the left side, and later the increase in fat became more general. Unilateral dystrophy in pituitary disease is not limited to fat. Ilbert Hancock reported a case of a girl ten years old, who had an hypophyseal tumor with obesity and right temporal hemianopsia. There was skeletal overgrowth of the left side involving the face, chest, arm and hand, leg and foot. And Biedl(*c*) reported a case of unilateral (left side) acromegaly. The condition began as a gradual enlargement of the left arm during the fourth year; other symptoms were sudden loss of vision, pain in legs, fever, and anuria, which were regarded as being due to acute meningeal or cerebral disturbances. Anatomical alterations of the sella were not demonstrable by X-ray. No satisfactory explanation has been offered for these unique conditions. They obviously cannot be due solely to hormone factors.

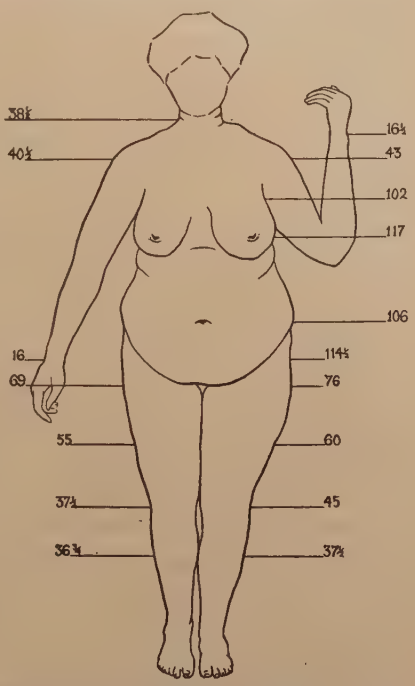


Fig. 24. Unilateral dystrophy of fat in a case of hypopituitarism.

General Pressure Symptoms

Psychic Disturbances.—Manifestations of psychic disturbances may result (1) from increased intracranial pressure, especially from a growth involving the temporal and frontal lobes, and (2) from insufficient glandular secretion. Some of the former have been enumerated under neighborhood symptoms, but in addition states of excitement, depression, psychoneurosis, and even hallucinations may develop. Lassitude, torpidity, and drowsiness are among the earliest symptoms.

Lesions involving the frontal lobes gives rise to such symptoms as impairment of memory, disorientation, untidiness, apathy, and stupor. Children suffering with hypopituitarism are usually temperamentally dull and apathetic, and are backward in their studies. They are usually irritable and often have difficulties with their playmates because of their lack of self-reliance and self-control.

As a result of insufficiency of the pituitary gland mental symptoms frequently develop, which vary from a mild psychosis to advanced forms of epilepsy and insanity. Beverly Tucker ascribes to the pituitary certain psychoses of adolescence some of which he attributes to hyperpituitarism, others to hypopituitarism. The latter he divides into two groups. The commonest psychosis resembles dementia præcox. The preadolescent symptoms are negligible. The patients begin to be dull in their studies, seclusive, and self-absorbed. Repetition of movements is common; hallucinations and delusions may or may not be present. They have difficulty in expressing themselves in writing, and are usually unemotional and unaffectionate, and obstinate and irritable when disturbed. There is thickening and enlargement of the clinoid processes, but the sella is about normal in size. To another group belong those cases in which the psychosis is not very profound. It consists chiefly of irritability, mental dullness, tardiness, truancy, and general lack of ambition; and in some cases epileptiform seizures. Röntgenograms show a small crowded fossa. A special form of hypophyseal psychosis has been described with confusional states and narcolepsy as the chief symptom (Tom Williams). Other psychic manifestations are lack of emotional inhibition, highly excitable states alternating with sluggishness, frequently phobias and compulsions, and moral and sexual obliquities, characteristics modified by pituitary feeding (Timme(*b*)).

The narcoleptic attacks are not attributed to a secretory disturbance of the pituitary gland. They are a part of a syndrome in which symptoms of cardiovascular irregularities occur; namely, tachycardia, arrhythmia, extrasystoles, embryocardia, and hypertension in addition to polyuria and polydipsia; according to the experimental observations of Ashner(*a*), J. Camus and G. Roussy(*a*) the entire syndrome can be produced

by excitation of the tuber cinereum and infundibulum. This view is supported clinically by a case in which at autopsy the hypophysis was normal, but a tumor of the third ventricle was found.

It has also been shown experimentally, that if the whole gland or a very large portion of it be removed, profound somnolence is apt to develop. This is associated with a subnormal temperature, slowing of the pulse and respiration, and diminished sensitiveness to pain, symptoms which frequently improve on the administration of pituitary gland substance.

Somnolence has a tendency to occur periodically, sometimes daily aside from the habitual sleeping hours, and then again with days intervening during which they respond fairly normal, and the sensorium is reasonably clear. It is this condition which suggested the possible relationship between the function of the hypophysis and hibernation in animals as first pointed out by Gemelli (1906) and later emphasized by Cushing(*b*). Persistent yawning, which often accompanies drowsiness, is a characteristic feature. The entire syndrome of somnolence, yawning, dullness, apathy, etc. with the presence of a clear sensorium shows a striking analogy to that of encephalitic lethargica. The fluctuating character of the former and the mode of onset are the chief differentiating features.

Epilepsy.—Attention has been called by Cushing to the relation of epileptiform seizures to lesions producing hypopituitarism. The so-called uncinate attacks are caused by a lesion extending into the interpeduncular region, producing pressure on or irritation of the uncinate gyrus. The aura is characterized by hallucinations of taste and smell. Sometimes the gustatory and olfactory phenomena with temporary loss of memory constitute the attack; at other times the attacks are more complete with marked convulsive seizures. General epileptiform seizures, which occur without uncinate factors, are probably due to glandular insufficiency, the result of hypoplasia.

On the relation of epilepsy to pituitary disorders the following is quoted from Cushing(*b*). "One may reassemble the data in regard to the possible relation of hypophyseal insufficiency to epilepsy as follows:

"1. Horsley, it will be recalled, in his first experimental hypophysectomies in the canine, observed no postoperative changes whatsoever in the condition of the animals. They were, however, used subsequently as subjects of cortical stimulation, and he noted that the motor cortex was unusually excitable.

"2. As already stated, we have observed a tendency to epileptiform convulsions in a number of our animals kept for long periods after partial hypophysectomy—animals that ultimately exhibited symptoms which we attribute to glandular insufficiency.

3. The study of a series of cases of hypophyseal disease in man has shown that epilepsy—a symptom unobserved in states of hyperpituitarism

—is a frequent accompaniment of clinical conditions in which an insufficiency of the gland is manifest. Moreover, that the brain, under these circumstances, is possibly overexcitable is suggested by the number of individuals in whom gustatory attacks have occurred under the influence presumably of a direct local irritation of the adjacent uncinate cortex by the enlarged gland.

4. As is well known, epilepsy is a frequent sequel of cranial injuries. In certain types of injury, as the common bursting fractures of the base, the pituitary body is prone to be damaged.

5. If, as we believe to be the case, the posterior lobe secretion normally enters the cerebrospinal fluid and thus comes to be in solution in a fluid which subsequently bathes the cortex, it is possible that its diminution from hypophyseal disease or injury may unfavorably affect the activity of the cortical cells. On this basis it is conceivable that a local scar which involves, or a tumor which presses upon, a given area of the cortex, may prevent the access to the cells of a substance which is essential to their functional stability.

6. Many individuals, supposed to be suffering from so-called genuine or essential epilepsy, present manifestations of a nutritional disorder—a tendency to adiposity and a high sugar tolerance, coupled with a lowered temperature and pulse rate—closely akin to the constitutional state which characterizes hypophyseal deficiency. In some of these individuals the administration of hypophyseal extract has served to moderate the seizures from which they previously suffered."

Johnston—basing his opinion on the X-ray findings of the sella turcica—states that the factor chiefly concerned in a certain group of cases of epilepsy is a mechanical one. The small roofed sella which encroaches upon the gland interferes with the normal blood supply and physiological activity, in consequence of which the animal economy is deprived of those substances produced within the pituitary necessary to stimulate normal metabolism. He substantiates his view by the fact that these cases are benefited by pituitary feeding, and suggests that relief might follow the resection of the clinoid processes; in other words, by a sellar decompression. Numerous other researches have been made along this line, the results of which are too vague and indefinite to enumerate.

Etiology

A review of the earlier literature gives one the impression that the chief etiological factor in dystrophia adiposogenitalis is either a tumor of the hypophysis or in close proximity to it. Subsequent reports, however, indicate that various other factors are concerned in the etiology, and that hypophyseal tumors play a minor rôle, especially in their relation to the

incidence of the disease; therefore, from a pathogenetic standpoint the causes may be grouped as neoplastic and aneoplastic.

There are unquestionably many mild cases—formes frustes—belonging to the second group, which do not present a complete clinical picture of the classical syndrome, but which nevertheless come under the caption of dystrophia adiposogenitalis. Reasoning a priori it is natural to assume that the milder manifestations, which depend upon a quantitative functional disturbance, occur relatively much more frequently than the severe manifestations which depend upon an almost completely arrested function. In some of these cases the gland is undersized, being encroached upon by the narrow confines of a pathologically small sella, and roofed in by the enlargement of the clinoid processes. Again others may show a normal sella. In either instance neighborhood symptoms are absent. An example of the latter is Cushing's(*b*) case of a girl fifteen years of age, weighing 239 pounds (having gained 124 pounds in 14 months), whose chief complaint was headache, obesity, and weakness, with a tendency to amenorrhea and infantile genitalia. There were no neighborhood symptoms; the sella was normal, carbohydrate tolerance was increased, thermic reaction was positive, and there were characteristic cutaneous manifestations.

It is also a well known fact that hypopituitary states frequently occur secondary to functional disorder in the pituitary itself (hyperpituitarism) or are associated with functional insufficiency of other internal secretory glands, especially the thyroid and sex glands, which may be primarily involved. Thus, in tracing the cause of hypopituitarism it is necessary to ascertain, if possible, whether the effects were primarily produced on the pituitary or secondarily through the medium of other glands; i. e., thyroid, gonads, thymus, adrenals, etc. This interrelation and interaction of the glands mentioned led to the designation Insuffisance Pluriglandulaire by the French authors Claude and Gougerot (1907); a clinical condition which has now become generally recognized, and recently much elaborated by Timme(*a*) and others.

Predisposing Factors: *Heredity.*—There is unquestionably an inherited tendency in certain families toward the development of endocrinopathies, which to some extent follows the Mendelian laws.

Heredity as a factor has been observed in goiter, myxedema, cretinism, diabetes, gigantism, and Addison's disease. Because of the analogy between the thyroid and pituitary it is reasonable to suppose that the same hereditary tendencies obtain in both glands. Definite data on this point are, however, meager.

It is known that cretins may be born from mild cretinous parents, or from goitrous parents. Paterson reported a family in which the first two children were cretins, the third child born was normal, the mother having taken thyroid from the third month of pregnancy. Moebius might

have made the same reference to the pituitary which he made to the thyroid, when he stated that the occurrence of simple goiter, often unnoticed, among the relatives of patients is suggestive of congenital alteration of the thyroid; a condition which can be converted into exophthalmic goiter by the influence of infection—typhoid fever, syphilis.

In my series of hypopituitary cases the hereditary character was observed in several instances. Thus, in one family the mother presented a typical picture of hypophyseal dystrophy. Three daughters and one son showed evidence of the disease in addition to thyroid deficiency. Two of these had mental symptoms for which they were treated in a psychopathic institution.

Another instance was that of a mother and daughter. The mother was a typical case of dystrophia adiposogenitalis. The daughter manifested symptoms before puberty—obesity and delay of menstruation until sixteen years of age—later, after marriage, menstruation ceased and the abdomen became large and protuberant—a phenomenon which she attributed to pregnancy. An examination at the end of the eighth month revealed the fact that she was not pregnant and the uterus and ovaries were of infantile size. Further investigation showed that she was also a case of true dystrophia adiposogenitalis.

Age.—In many cases there is a congenital predisposition. The disease frequently begins at puberty or during the third decade. One-third of the published cases occurred between thirty and fifty years of age, and one-tenth between fifty and sixty (v. Frankl-Hochwart).

Sex.—The disease appears relatively much more frequent in the female than in the male. This is no doubt due to the fact that the female is peculiarly subjected to disorder of the endocrin system through the special function pertaining to menstruation, reproduction, and the menopause. In tumors of the pituitary gland the distribution between the two sexes is about even.

Congenital Hypopituitarism.—Although there are no authentic reports of cases of congenital hypopituitarism, Priesel considers that such do occur in the form of hypophyseal dwarfs, which he divides into two forms; 1. Primordial—in which the individual is subnormal at birth and develops symmetrically, and 2. Infantile—in which the individual is normal at birth, but growth becomes retarded between the fifth and fifteenth year.

Among predisposing factors of a congenital nature may be mentioned:

1. Developmental abnormalities—either osseous, influencing the size and shape of the sella turcica, or glandular through embryonic defect in which the pituitary is imperfectly developed.
2. Syphilis—Simonds, who reported a case of congenital syphilis of the hypophysis, found ten cases in the literature. Indi-

rectly syphilis is undoubtedly responsible for many cases. In fact, Peritz(*b*) is of the opinion that syphilitic hydrocephalus is the most frequent cause of hypophyseal lesion.

Trauma is an occasional factor as demonstrated by Madlung's case so often quoted. The case is that of a girl 9 years of age in which a bullet lodged in the sella turcica, producing all the symptoms of dystrophia adiposogenitalis.

In six of Cushing's hypopituitary cases early symptoms were apparently incited by trauma. Five of these cases were associated with tumors.

Alterations at the Physiological Epochs.—Owing to the normal physiological alterations, associated with puberty in both sexes, and menstruation, pregnancy, lactation and the climacteric in the female—functions regulated and controlled through the endocrin system—individuals are particularly prone during these epochs to develop certain endocrinopathies, especially those referable to the pituitary, thyroid and gonads. This is due to the direct influence of the interstitial cells of the testes and ovaries upon the pituitary and thyroid functions.

According to these sex epochs Schumann classifies dystrophia adiposogenitalis in women into three groups.

1. Hypopituitarism before puberty, corresponding to Fröhlich's type.
2. Hypopituitarism appearing after sexual activity has developed, frequently beginning during the period of betrothal and reaching its height in the month immediately following marriage. The condition continues unchanged from two to five years when either spontaneous improvement takes place or develops into the adipose-infantile-sterile type of "fat women."
3. Hypopituitarism in normally matured women with normal menstruation, who have borne one or more children. After the birth of the last child there occur lactation atrophy, superinvolution of the uterus, amenorrhea, obesity, excessive carbohydrate tolerance with cirrhotic changes in the ovaries and atrophy of the uterus.

In one of the writer's most typical cases of hypopituitarism with well marked fat dystrophy—girdle type—symptoms began to develop almost immediately after a course of radium treatment for uterine fibroid (Group A, Case VIII.)

Infections play an important etiological rôle. Histological changes in the hypophysis have been observed in individuals who died from infection (Delille). Experimental infection on animals produced similar changes. These consist of hyperplasia of either the anterior or posterior lobe, depending upon the nature of the organism. The effect which acute infectious diseases (e. g., typhoid and rheumatic fever) have upon the thy-

roid and adrenals is common knowledge. That of chronic infections is, perhaps, not so well understood, although they tend to glandular degeneration with sclerosis, which should lead to hypofunction with its concomitant syndromes. Chronic infections have been recognized as a factor in thyroid deficiency. They occurred in seventy-eight out of one hundred cases studied by the writer. From an analysis of forty-six cases of hypophyseal dystrophy it appears that chronic infections play even a more conspicuous rôle in pituitary deficiency. Forty-two of the cases were associated with chronic infectious processes. Chronic appendicitis and cholecystitis occurred in twenty-two cases, in three of which both conditions existed. Chronic tonsillitis occurred in twenty cases and alveolar infection in thirteen. A history of malaria was recorded in four cases. The incidence of these infections certainly suggest more than a casual relation to hypopituitarism. The acute infections which occurred in the series include typhoid, grippe, pneumonia, rheumatic fever, meningitis, etc.

Attention has been called by Massalongo and Piazza (1914) to post-infectious dystrophia adiposogenitalis, reporting an interesting case following a severe pneumonia and citing two cases following typhoid, in which degeneration or sclerosis of the gland was found.

Cushing(*b*) noted the incidence of acute infectious processes in at least seven of his cases in most of which symptoms of primary hyperpituitarism were exhibited. A case of acute suppurative hypophysitis was recently reported by Boggs and Winternitz.

Guerrini found histological changes in the pituitary gland as a result of a reaction to acute and chronic intoxications, e. g. pilocarpin, ichthyotoxin, diphtheria toxin, and endogenous toxin. These effects are quite similar to those produced upon the thyroid by various sorts of intoxication which have been reported by Roger and Garnier, de Quervaine and Martini.

New Growth

For our first description of an associated obesity with an hypophyseal tumor credit must be given to Mohr (1840). However, it was not until about sixty years later that definite clinical syndromes were recognized as the result of such tumors. Since then hundreds of cases of new growth of various kinds have been reported.

The simplest form of growth is probably a diffuse hyperplasia arising from a functional overgrowth, such as occurs in the advanced form after multiple pregnancies (Ewing). These may regress but some probably pass into a malignant form of adenocarcinoma. The condition of hyperplasia, like in the thyroid, is often associated with adenoma; unquestionably many cases regarded as tumors are simple hyperplasia.

In a cursory review of the literature the following varieties of hypophyseal lesions have been encountered, namely, adenoma, glioma, psammona, metastatic carcinoma, adenocarcinoma, teratoma, sarcoma, angioma, cystoma, steatoma, chondroma and fibroma; other lesions include gumma, tubercles, embolism, trauma, hydrocephalus, etc. In Frankl-Hochwart's collection of cases without acromegaly there were

27 sarcomata
15 cysts
43 adenomata
12 carcinomata
9 strumata
7 tubercles
3 gummata
3 gliomata
2 teratomata
1 steatoma
1 chondroma
1 fibroma
1 unidentified

Diagnosis

The diagnosis of dystrophia adiposogenitalis—typus Fröhlich—is ordinarily not difficult. The triad upon which the syndrome is based consists of obesity, skeletal undergrowth and hypogenitalism. To complete the clinical picture alterations in the sella turcica and neighborhood signs and symptoms, including distortion of the visual fields, should be added.

However, such a classical illustration is not presented in the average case. Variations occur either owing to the absence of some of the above mentioned symptoms or to additional features not embraced in the typical syndrome. These include (a) atypical forms, (b) early cases, (c) milder types, and (d) pluriglandular varieties in which the hypophyseal symptoms predominate.

(a) Examples of the *atypical form* are some of the hypophyseal dwarfs (Lorain type) in which there is marked skeletal undergrowth and infantile genitalia but without obesity. In other instances there may be enormous obesity and genital hypoplasia with skeletal overgrowth. Illustrative of this form is Griffith's case of a boy eleven years old with all the characteristics of Fröhlich's syndrome except the skeletal. He was 5 feet and 1 inch tall (8 inches above normal for his age) and weighed 251 pounds with an abnormally small sella and high sugar tolerance. Hypopituitary dystrophy secondary to hyperpituitarism (gigantism, acromegaly) presents an atypical appearance owing to the enlargement of the acra (nose,

lips, tongue, mandible, hands and feet) and hypertrophic changes in the bones. Many of these cases should be regarded as states of dyspituitarism.

(b) In the *early stages* of dystrophia adiposogenitalis the symptoms are not sufficiently outspoken to make an absolute diagnosis. The condition should be suspected in children with a developing obesity in which growth has become arrested, especially if associated with psychopathic tendencies and frequent headache.

Attention has already been called to the influence of the various physiological epochs, puberty, pregnancy, and menopause. It is usually at these periods when the pituitary undergoes histological changes, associated with alteration of function that the early symptoms manifest themselves, therefore considerable importance should be attached to delayed puberty, obesity and amenorrhea following pregnancy, and obesity, sluggishness, torpor, and headaches following the menopause.

(c) In the *milder forms* emphasis should be laid upon the type of fat distribution, which is one of the most characteristic of symptoms; even if the obesity is slight, the tendency to fat deposition in localized areas is evident. The condition and distribution of the hair and the texture of the skin should always be considered conjointly with the adiposity. A history of sexual abnormalities—impotence, absence of libido, amenorrhea and sterility—can frequently be elicited, although genital atrophy is not always present. Biedl(*c*) found it in only 12 out of 32 of his milder cases.

(d) *The pluriglandular varieties* are of common occurrence. Only those cases in which the pituitary factor is primary or predominates the clinical picture should be considered in connection with dystrophia adiposogenitalis; symptoms referable to the deficiency of the thyroid, gonads, and adrenals must be differentiated.

Some of the most valuable data for the purpose of diagnosis are those derived from X-ray studies for abnormality of the sella turcica and the epiphyses. The presence of neighborhood signs and symptoms (optic nerve lesion and visual field defects) and increased sugar tolerance, are also of great diagnostic importance. The existence of any or all of the above findings, in addition to other symptoms enumerated, furnish convincing proof of a correct diagnosis. Ophthalmological conditions play an important rôle in diagnosis, especially for localization of tumors, while other symptoms which result in consequence of local or general pressure, such as headache, nausea, vomiting, epileptiform seizures, stupor, narcolepsy, trophic disturbances, polyuria, amenorrhea etc., are more of a general nature. Moreover in slowly growing tumors there is a compensatory reaction to the gradual pressure, so that the general symptoms are in abeyance. In these cases the ocular manifestations are of the greatest significance.

Thyroid.—In thyroid deficiency (myxedema) the obesity is more general; the skin is thick, infiltrated, non-transparent, wrinkled, dry and

desquamating; the fingers are short, thick and often broad at the ends; the face is round, lips thick, and expression dull.

Gonads.—The most difficult problem encountered in diagnosis is the differentiation between a certain class of cases of hypophyseal dystrophia adiposogenitalis and the adiposogenital dystrophy of the eunuchoid type. The fact that genital atrophy has been regarded by some authors (Schüller(*b*); Tandler & Gross) as the primary cause of Fröhlich's syndrome, and that the type of obesity is identical in the two conditions (van Noorden) suggests close similarity. Falta(*c*) divides dystrophia adiposogenitalis into two clinical groups—the primary hypophyseal and the primary eunuchoid. The eunuchoid grows tall (above the normal average size), the extremities are disproportionately long, so that the distance from the symphysis pubis to the heel is longer than the rest of the body. Hypopituitary individuals are usually below normal in height, and the distance from the top of the head to the symphysis is longer than the lower extremities, measured from the symphysis. Brain pressure symptoms and sellar deformation are absent in eunuchoidism, and the epiphyseal junctures remain open much longer than they do normally or in hypophyseal dystrophy. Eunuchoidism is always associated with genital hypoplasia, which is frequently absent in hypophyseal dystrophy.

Adrenals.—The asthenia, low blood pressure, and pigmentation associated with hypopituitarism have been ascribed to hypoadrenia—the suprarenal glands in these cases have been found to be very small.

Pineal.—A form of obesity resembling dystrophia adiposogenitalis occurs in lesions of the pineal gland. Cerebral, local and general, pressure symptoms occur similar to those of pituitary origin. These cause visual disturbance, stupor, mental disturbances, epileptiform seizures, polyuria, and genital dystrophy. The chief differentiating feature is that the genital dystrophy results in hypergenitalism with excessive growth of pubic and axillary hair.

Adiposis dolorosa (Dercum's disease) and dystrophia adiposogenitalis have many points in common. The cardinal symptoms of the former (viz., adiposity, pain, asthenia, psychic disturbance) may all occur in the latter. The character of the obesity, which appears as large lipomatous masses often irregular in distribution and usually painful, is the chief distinguishing feature. The disease is probably of pluriglandular origin. Lesions of the thyroid, ovaries, and adrenals, as well as the pituitary, have been found at autopsy. Other forms of adiposes and lipomatoses occur, but these have no close resemblance to the obesity of dystrophia adiposogenitalis. Lyon (1910) reported a series of cases belonging to this group and gave a complete bibliography, and recently Sprunt (1920) revised and reviewed the subject up to date.

Prognosis

The prognosis depends upon the character of the lesion producing the syndrome of dystrophia adiposogenitalis. The outlook of patients suffering with hypophyseal tumors is grave, even in those with benign tumors. The operation itself is a formidable one and the death rate is high, especially in the hands of inexperienced cranial surgeons. However, favorable results are frequently obtained by operation, and the patients are occasionally symptomatically cured. The course is relatively slow, and, in some cases the symptoms may persist for a great many years.

Frankl-Hochwart, basing the prognosis on the history of the duration of the disease, states that of his 124 collected cases the course varied from several weeks to twenty years or more. Fifty per cent gave a history of from one to two years duration and sixty-one per cent less than three years.

In the milder types of the disease (aneoplastic forms) the prognosis is more favorable. This is particularly true of cases which manifest their first symptoms during the physiological epochs (puberty, pregnancy, parturition, menopause). The symptoms may subside spontaneously or be relieved by organotherapy.

The pluriglandular forms with predominant pituitary deficiency are also amenable to glandular therapy. Unless the syndrome is due to a tumor of the pituitary gland or local pressure the prognosis unquestionably is more favorable if the condition is recognized early and proper treatment inaugurated.

Treatment

The treatment of dystrophia adiposogentalis may conveniently be described under the following headings: (a) organotherapy, (b) irradiation, (c) general measures—diet, bath, exercise, massage, etc.—(d) surgical.

Organotherapy.—The advancement along the line of therapy in diseases of the pituitary gland has kept pace with the progress made in the study of its physiological activities and its symptomatic manifestations. Treatment has become more rational and the indications for organotherapy have been established on a more sound and scientific basis. Fundamentally organotherapy is intended to supply the organism with normal gland substance containing the active principles necessary to physiological growth development and metabolism. Hence it is in the deficiency syndrome that this plan of treatment is most efficacious. In dystrophia adioposogenitalis these include:

A. Anterior lobe deficiency.

1. *Disturbance of growth* (*skeletal defects*)
2. *Development of obesity* (*hypophyseal fat dystrophy*)
3. *Genital hypoplasia* (*infantile genitalia*)
4. *Temperature anomalies* (*hypothermia*)
5. *Cachexia hypophysopriva* (*apituitarism*)

B. Posterior lobe deficiency.

1. *Hypotension*
2. *Increased sugar tolerance*
3. *Diminution of basal metabolism*
4. *Asthenia*

Associated Symptoms the result of hypophyseal tumors include headache, vertigo, vomiting, visual defects, nervous and mental disturbances, and polyuria or diabetes insipidus. The latter, which was formerly attributed to posterior lobe deficiency, is not included in that group, owing to the result of the clinical and experimental investigations of Houssay, Leschke, and others previously mentioned.

Organotherapy.—Most of the symptoms of dystrophia adiposogenitalis, unless due to a progressive neoplastic growth, are favorably influenced by the administration of the hormones of the pituitary, thyroid and the gonads. The thyroid hormone is equally as important, if not more so than the pituitary. The ovarian and testicular have the least therapeutic effect.

The thyroid has been called a sex gland because of its accelerating influence on the function of the sexual organs. The presence of the thyroid hormone, as well as that of the pituitary, is essential to the normal development and function of the gonads. Moreover, it is the greatest stimulator of metabolism known, acting probably as a general protoplasmic stimulant. The thyroid also stimulates the pituitary function. It is thus easily conceivable how the administration of thyroid gland substance would favorably influence the various groups of symptoms due to pituitary deficiency in dystrophia adiposogenitalis.

Through its influence on metabolism it has a tendency to improve the fat dystrophy, decrease sugar tolerance and increase the rate of basal metabolism. The increased basal metabolic rate tends to restore the hypothermia, bradycardia, hypotension, dry skin, etc., to normal. Its accelerating influence on the functions of the pituitary and sex glands augment the effect of pituitary and ovarian gland substance upon genital hypoplasia and hypogonadism as well as on infantilism of hypophyseal origin.

The experimental production in animals of a syndrome corresponding to Fröhlich's by an almost complete extirpation of the anterior lobe of the pituitary, and the possibility of preventing the development of

this syndrome, after the operation, by injection or feeding anterior lobe substance certainly furnishes sufficient evidence to warrant the administration of anterior lobe substance in states of hypopituitarism. However, it is surprising, in view of these facts, that until quite recently few cases of dystrophia adiposogenitalis successfully treated with anterior lobe substance appeared in literature. This is probably due to the fact that only the severe and more advanced cases, usually of neoplastic origin, were formerly recognized, while the milder types, which are more susceptible to treatment were almost invariably overlooked.

Another difficulty formerly encountered was in grouping these cases. Many of them present pluriglandular manifestations which result from the reaction and interaction of the chain of ductless glands—notably the thyroid, sex glands, and adrenals. They frequently have a genital syndrome which may be primary or secondary, and symptoms referable to thyroid and adrenal insufficiency. In the writer's series of forty-six cases twenty-seven showed symptoms of varying degrees of hypothyroidism. De Camargo makes the broad statement that there is no such thing in pathology as monoglandular syndrome, for all endocrin syndromes are pluriglandular with predominance of one gland. Consequently a combination of the respective hormones, especially thyroid and pituitary, should yield better results in this class of cases than either one given singly.

Among the earlier investigators, who claimed to have seen good results follow the administration of hypophyseal substance in hypopituitarism, are Cushing(*b*), Levy and Rothschild, Delille, and Falta(*c*).

Pituitary extracts have been prepared in both dried and liquid form from the whole gland, the pars anterior and the pars posterior. These preparations are familiarly known by their trade names of which there are many. Bell(*b*) suggests as a convenient nomenclature pituitarin, hypophysin, and infundibulin respectively. The selection of the preparation used should depend upon the character of the symptoms. If there is marked evidence of involvement of both lobes, the whole gland substance is most suitable. If anterior lobe symptoms predominate, good results are obtained by extract of the pars anterior. With marked asthenia, hypotension, and high sugar tolerance the extract of the posterior lobe is indicated, although these cases often respond well to thyroid medication. The associated condition of diabetes insipidus can only be controlled by the injection of infundibulin.

As should be expected, not all cases respond favorably to treatment. This applies especially to those in which there is a progressive lesion of the pituitary gland or pressure from an adjacent tumor. Under these circumstances pressure symptoms can best be relieved by surgical measures (decompression, extirpation) although the deficiency syndromes are frequently benefited, at least temporarily, by organotherapy.

In my personal observation of a series of forty-six cases treated with gland substance twenty-six showed definite improvement, nine marked improvement, and eleven remained unimproved; in three of these eleven treatment was not continued long enough to determine its efficiency. Sufficient time has not elapsed to say whether the results in those benefited are permanent, although a number of these patients have had no treatment for three or four years, and have remained free from symptoms.

Organotherapy has a remarkable effect in redistributing the fat in dystrophia adiposogenitalis. My attention was directed to this phenomenon in 1915, in the case of a woman aged 41 years, married, weighing 125 pounds. She presented three fairly well defined symptom groups, viz.; those referable to pituitary insufficiency: fat dystrophy and genital hypoplasia; those referable to ovarian insufficiency: frigidity, sterility and amenorrhea; those referable to thyroid insufficiency: mental, neuromuscular and trophic skin disturbances. The patient was an invalid unable to attend to ordinary household duties on account of apathy, stupor and dullness and feeling of intense exhaustion.

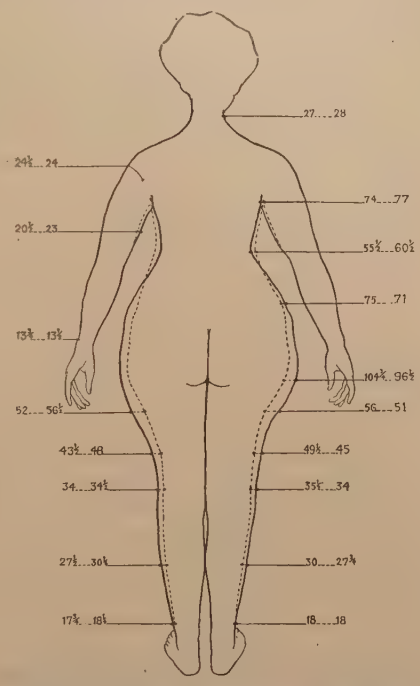


Fig. 25. Dark, continuous line and outside figures represent the body outline and circumference measurements recorded before treatment. The dotted lines and inside figures represent the same recorded 8 weeks later. GROUP A, CASE IV.

The most conspicuous symptom was obesity of the girdle type. She noticed an enormous increase in the size of her hips, buttocks and waist, and although she had gained about 20 pounds in 10 months there was no increase in the rest of her body. On the basis of a pluriglandular syndrome a combination of gland substance derived from the three respective glands was administered with striking results both in regard to her general condition and her obesity. The tremendous folds of fat rapidly disappeared in spite of the fact that she practically lost no weight. Frequent alterations of her clothes became necessary, and measurements as recorded by her dressmaker showed waist 30 inches, hips 43 inches before treatment; these decreased after eight weeks of treatment to 26 inches and 36½ respectively, and after eleven weeks of treatment to 25 and 35½ inches. Thus the waist measure decreased 5 inches, and the hips 7½ inches while the patient lost only one pound in weight. However,

TREATMENT OF CASES OF DYSTROPHIA ADIPOSOGENITALIS WHICH RESULTED IN TYPICAL FAT REDISTRIBUTION AS DETERMINED BY ACTUAL WEIGHT AND CIRCUMFERENCE MEASUREMENTS

Group A.

No.	Age	Sex and Station	*Treatment* Dosage daily amounts of gland substance, etc.	Height	Date	Weight	*Measurements in Centimeters*									Remarks
							Neck	Axillary	Waist	Umbilical	Hips	Thighs	Knees	Calves	Shoulders	
1	53	F/M	Anterior Pituitary Lobe gr. ii½ Thyroid gr. i	5′ 3″	10-12-18	132	....	81.5	70.5	....	101	.....	....	....	....	Hypophyseal dystrophy with thyroid deficiency. Hypertension, cardiac hypertrophy and hypertrophic arthritis.
					1-1-19	125	....	84	71 ′	....	96	.....	....	....	....	All these conditions improved with the disappearance of the abnormal deposits of fat.
2	34	F/M	Anterior Pituitary Lobe gr. ii½ Thyroid gr. ii	5′ 4½″	3-2-17	180	35	93.5	83.5	....	110	65	....	....	....	General adiposus, except face, forearms, hands and feet.
					4-9-17	173	35	98	80	....	107.5	62.5	....	....	....	Bradycardia and hypothermia: improved.
3	43	M/M	Anterior Pituitary Lobe Thyroid Mixed gland Varying doses	5′ 8½″	9-29-17	150	34.5	81	82.5	96	96	R-55.5 L-52	....	....	....	Dystrophia adiposogenitalis (Typus femininus). Genital hypoplasia, cryptorchidism-psychosis, etc. Amelioration of symptoms followed the redistribution of fat.
					11-22-17	153	34.5	87.5	81	85	93.5	R-53 L-52	....	....	....	
4	25	F/S	Anterior Pituitary Lobe gr. v Thyroid gr. ii	5′ 6″	1-2-20	181	37.5	85	75	....	108	63.5	44.5	....	....	Dystrophia adiposogenitalis and hypothyroidism; closed in sella-pituitary headaches.
					2-7-20	171	34.5	86	81.5	....	101	58.5	37	....	....	Trophic disturbance of fat, hair and nails. Amenorrhœa. Remarkable improvement.
5	35	F/M	Thyroid gr. i Sodium Cacodylate gr. iii every 3 days Later Anterior Pituitary Lobe gr. ii ½	5′ 7″	4-16-20	160	31.5	83.5	69	....	102	.....	....	....	....	Fat dystrophy of hypophyseal type with sterility.
					7-7-20	158	33	84	68	....	107	.....	....	....	....	Improved.
6	42	F/S	Appendectomy Anterior Pituitary Lobe gr. ii½ Thyroid grs. iii	5′ 3¾″	12-8-15	118	27	74	55.5	75	104.5	56	....	....	....	Dystrophia adiposogenitalis associated with hypothyroidism and genital syndrome. Dullness, stupor, languor, sterility, amenorrhœa, temporal headaches and marked hypophyseal dystrophy.
					2-6-16	121	28	77	60.5	71	96.5	51	....	....	....	Fat redistributed and general condition improved. Fat reaccumulated 6 mos. after discontinuing treatment. (See Fig. 23.)
7	32	F/M	Thyroid gr. i-ii Diet and Exercise	5′ 2″	4-1-19	159	Bust	106	82.5	....	115	.....	....	....	....	Fat dystrophy of hypophyseal type with sterility and amenorrhœa. Condition favorably influenced by thyroid. No other organotherapy.
					7-1-20	148		106	72.5	....	100	.....	....	....	....	

8	56	F/M	Thyroid gr. i½ Anterior Pituitary Lobe gr. ii½	5′ 2½″	9-25-19	125	29	75	62	....	100.5	54	34	33.5	28.5	Fat dystrophy with hypophyseal symptoms developed after 4 months radium treatment for uterine fibroids. The waist increased 2½ inches, hips 3 inches, but the chest, arms and neck were not affected. Symptoms and fat dystrophy relieved by thyroid and anterior pituitary lobe. When treatment was discontinued the symptoms returned within three weeks and the fat dystrophy within four months.
					11-20-19	126	30.5	76	63	....	92	52	32.5	31.5	30.5	
9	52	F/M	Tablet Hormotone iii Pituitary Whole Gland (Armour) Caps. iii No tolerance for Thyroid	5′ 4″	12-31-16	159	31.5	83	66.5	....	110	63.5	....	....	....	Hypopituitarism with marked fat dystrophy. Severe headaches and enlarged sella. Responded favorably to treatment.
					2-19-17	149	30.5	86.5	66	....	105	61.5	....	....	....	
10	29	F/M	Tablet Hormotone iii-iv Later Thyroid gr. iv	5′ 6½″	5-28-15	163	....	86	75	....	106.5	62	45.5	....	....	Symptoms of both hypopituitarism and hypothyroidism. Pulse which was 105 and irregular reduced to 86 and became regular. Constipation was relieved and nervous symptoms improved.
					8-19-15	159	....	86.5	73.5	....	104	58	40	....	....	
11	46	F/M	Anterior Pituitary Lobe gr. v	5′ 2″	1-1-16	111	28.5	71	61	....	95.5	54	32.5	....	....	Family history of obesity of the hypophyseal type. Whenever weight increased an abnormal deposit of fat appeared about the hips, upper thighs and lower abdomen. Configuration of the body restored to normal with anterior pituitary lobe.
					2-6-16	112	29.5	72.5	64	....	94	52.5	31.5	....	....	
12	26	F/S	Thyroid gr. iv Anterior Pituitary Lobe gr. v	5′ 4″	3-13-20	218	34	95.5	94	....	129.5	76	....	....	....	Within the past 6 years weight increased from 130 to 218 pounds. Fat deposited as large cushions over gluteal region and abdomen. Headaches and amenorrhœa developed. This case responded well to treatment.
					7-3-20	205	34.5	98	92	....	126	74	....	....	....	
13	30	F/M	Tablets Hormotone ii	5′ 1″	7-13-20	136	32	80.5	67.5	....	103.5	65	....	....	....	Chief symptoms: headache, neuromuscular pains and obesity of the hypophyseal type. Hip measurements decreased and weight increased.
					7-28-20	139	32	82	69.5	....	102	63	....	....	....	
14	21	F/M	Thyroid gr. ii Anterior Pituitary Lobe gr. ii½	5′ 2″	2-2-16	110	....	74.5	63	....	95	.....	....	....	....	Patient complained for 7 years with deep frontal headache. The sella was large and deformed. There was an excessive accumulation of fat about the hips and upper thighs. Condition improved.
					3-14-16	108	....	76	67	....	88	.....	....	....	....	

TREATMENT OF CASES OF DYSTROPHIA ADIPOSOGENITALIS WHICH RESULTED IN TYPICAL FAT REDISTRIBUTION AS DETERMINED BY ACTUAL WEIGHT AND CIRCUMFERENCE MEASUREMENTS (*continued*)

Group A (continued)

No.	Age	Sex and Station	*Treatment* Dosage daily amounts of gland substance, etc.	Height	Date	Weight	*Measurements in Centimeters*									Remarks
							Neck	Axillary	Waist	Umbilical	Hips	Thighs	Knees	Calves	Shoulders	
15	24	F/S	Antiluetic Anterior Pituitary Lobe Thyroid Varying doses Pituitrin	5′ 3′	11-28-16	129	32	80	69.5	78	99.5	59.5	35	33.5	....	Typical Fröhlich syndrome with diabetes insipidus and amenorrhœa. Positive Wassermann. Cranial bone changes. Closed-in sella.
					12-12-16	129	30.5	81.5	71.5	79	98	59	35	33	....	Some improvement at first. Died two years later in state of narcolepsy. Pituitrin 1 c.c. daily controlled polyuria.
16	25	F/M	Anterior Pituitary Lobe gr. v	5′ 5″	6-22-20	197	34	95.5	88.5	....	120	R-73 L-66.5	....	....	....	Irregular distribution of fat: Hypophyseal type. Breasts very large, right hip much larger than left. Condition favorably influenced.
					7-26-20	189	34.5	99.5	83	....	113.5	R-66.5 L-60.5	....	....	....	

TREATMENT OF CASES OF DYSTROPHIA ADIPOSOGENITALIS WHICH RESULTED IN TYPICAL FAT REDISTRIBUTION AS DETERMINED BY ACTUAL WEIGHT AND CIRCUMFERENCE MEASUREMENTS

Group B

No.	Age	Sex and Station	*Treatment* Dosage daily amounts of gland substance, etc.	Height	Date	Weight	*Measurements in Centimeters*									Remarks
							Neck	Axillary	Waist	Umbilical	Hips	Thighs	Knees	Calves	Shoulders	
1	36	F/M	Thyroid gr. i Anterior Pituitary Lobe gr. ii½	5′ 7¼″	3-1-20	165	36.5	91	75.5	99.5	110	65	....	....	....	Dystrophia adiposogenitalis with a very small closed-in sella pituitary type of headache and amenorrhœa.
					4-30-20	167	34.5	91	78.5	98	106.5	68.5	....	....	....	Improved.
2	42	F/S	Thyroid gr. ii Mixed Gland B. W. & Co. Tablet ii	5′ 6″	3-11-19	181	....	92.5	77.5	....	105	62.5	40	37.5	35	Acra and skeletal features suggest acromegaly. Obesity and symptoms are those of hypopituitarism which is probably secondary.
					5-9-19	182	....	92.5	77.5	....	105	62.5	40	35.5	35	Improved.
3	28	F/S	Anterior Pituitary Lobe gr. v Later Thyroid gr. i Tablet Hormotone iii	5′ 3½″	3-2-17	160	35	95	80	....	111.5	64	41	37	35.5	Dystrophia adiposogenitalis with characteristic distribution of fat.
					4-9-17	156	35.5	91	78	....	102.5	61	34.5	35.5	33.5	The reduction of fat was general on organotherapy and symptoms improved.
4	39	F/M	Thyroid gr. ii Anterior Pituitary Lobe gr. vii ½	5′ 5″	7-21-17	177	35	94	83	....	112.5	64	42	....	36	Pluriglandular obesity (pituitary, thyroid and ovarian). No menstruation for 3 years, visual hallucinations, mental dullness, languor, neuromuscular pains, etc. All measurements decreased.
					8-10-17	160	34	90	80	....	105.2	62	41	....	34	Condition improved.
5	32	F/S	Thyroid gr. i½ Sodium Cacodylate gr. iii every 3 days	5′ 5″	3-15-20	134	35	81.3	70	....	97.5	57.5	....	....	....	Hypophyseal dystrophy with mild hypothyroid symptoms. The latter were relieved by thyroid which had no effect on the adiposus.
					4-3-20	135	35	80	70	....	96	57.5	....	....	....	
6	45	F/S	Tablet Hormotone iii Thyroid gr. iii	5′ 3″	7-24-15	175½	31	92	97	....	117	66.5	43	36.5	....	Hypopituitarism with hypothyroidism. Fat chiefly accumulated below the waist and legs were relatively large.
					8-20-15	163	31.5	91	83.5	....	113	63	37.5	35	....	Patient improved.
7	22	F/S	Thyroid gr. ii Anterior Pituitary Lobe gr. v	5′ 2″	4-22-16	138	32	87	71.5	....	102.5	61.5	....	....	....	Thyroidectomy for goitre was followed by thyroid deficiency and later fat dystrophy of the hypophyseal type with large folds of fat in the gluteals and upper thighs.
					5-22-16	138½	32	86	70	....	105	61.5	....	....	....	Treatment had no effect on fat dystrophy.

TREATMENT OF CASES OF DYSTROPHIA ADIPOSOGENITALIS WHICH RESULTED IN TYPICAL FAT REDISTRIBUTION AS DETERMINED BY ACTUAL WEIGHT AND CIRCUMFERENCE MEASUREMENTS (*continued*)

Group B (continued)

No.	Age	Sex and Station	*Treatment* Dosage daily amounts of gland substance, etc.	Height	Date	Weight	*Measurements in Centimeters*									Remarks
							Neck	Axillary	Waist	Umbilical	Hips	Thighs	Knees	Calves	Shoulders	
8	41	F/M	Thyroid gr. iii-iv Anterior Pituitary Lobe gr. ii½	5′ 5½″	3-22-20	285	39	121	115.5	....	144	75	....	....	....	Enormous obesity with tremendously enlarged hips and abdomen. Hypothyroid syndrome, amenorrhœa, etc.
					4-9-20	272	39	117	104.5	....	137	86	....	....	....	General health much improved.
9	33	F/M	Thyroid gr. ii Anterior Pituitary Lobe gr. v Massage Exercise	5′ 8¼″	3-11-20	221	40	96.5	94	....	130	75	....	....	....	Pluriglandular syndrome (thyroid, pituitary and ovarian).
					6-14-20	220	39	94	96	....	130	70	....	....	....	Ovarian cyst—panhysterectomy and thyroidectomy. Treatment not effectual.
10	20	F/S	Thyroid gr. i½ Anterior Pituitary Lobe gr. ii½	5′ 5″	7-3-20	186	37.5	92.5	80	....	107.5	67.5	....	....	....	Generalized adiposis with preponderance over hips, thighs and abdomen.
					7-31-20	178	35	90.5	77	....	107	67.5	....	....	....	The upper circumferences decreased; the lower remain stationary which is contrary to the general rule.
11	16	F/S	Tablet Hormotone ii Sodium Cacodylate	5′ 2¾″	7-1-19	122	30.5	78.5	63	74	96	R-59 L-56.5	36 37	33 33.5	....	Hypophyseal symptoms with local accumulations of fat affecting the right side more than the left—especially the breast and hip.
					8-12-19	121	30	78	62	71	93	R-58.5 L-56.5	35 34	32.5 33.5	....	
12	53	F/M	Anterior Pituitary Lobe gr. ii½ Thyroid gr. iii	5′ 5″	1-26-16	193	36.5	98	91.5	....	122	R-62.2 L-56	40 41.5	36 34.2	32 23½	Obesity associated with symptoms of hypothyroidism and hypopituitarism with unilateral increase of right side.
					3-11-16	197	36.5	91	91	....	120.5	.....	....	....		

there was a perceptible increase of subcutaneous fat over the chest, shoulders, neck and face. The patient completely recovered, and her health and figure were normal four years after treatment was discontinued.

For the purpose of ascertaining the nature and extent of fat redistribution in dystrophia adiposogenitalis a system of measurements combined with the weight of the patient has been employed in the series of cases studied and tabulated in Groups A and B. The circumference measurements are indicated in Figure 25. The most important are the axillary, waist, hip and thigh measurements. The axillary circumference is taken at the level of the axillary folds, and the thighs at the juncture of the groins. The waist and hip are taken without regard to any fixed level or anatomical landmarks. The former represents the minimum circumference of the upper abdomen and the latter the maximum at any point below the umbilicus; a point which fluctuates as much as three or four inches, depending upon the degree of girdle adiposity. The maximum hip circumference occurs at a much lower level in well marked cases of girdle obesity than it does in the milder forms, but during the process of fat redistribution this level is gradually raised.

Out of a series of 46 cases 28 have been studied with reference to the effect of organotherapy upon fat redistribution, combining both mensuration and weight as criteria in determining the results.

The cases have been divided into two groups. Group A (16 cases) represents those in which the results have been designated as typical fat redistribution, i. e., the upper circumference measurements increased and the lower diminished. In group B (12 cases) appear the atypical cases, including those with irregular redistribution as well as those uninfluenced by treatment. Those which failed to respond to treatment did not present a well defined clinical picture of dystrophia adiposogenitalis. In some of them the predominant symptoms could be attributed to other endocrin glands (e. g., cases 5, 7, 9, 10 of Group B). It would thus appear that anterior pituitary and thyroid feeding could be used advantageously as a therapeutic test for diagnostic purpose. In true cases of dystrophia adiposogenitalis the effect of thyroid and anterior pituitary substance upon fat dystrophy can be disclosed by mensuration usually within a period of two weeks. With the improvement of the obesity a coincident improvement of the general condition of the patient was almost invariably observed, (Fig. 26.) The nervous and mental symptoms subsided; fatigability diminished; metabolic processes increased; and the sexual functions were often restored to normal—results which are not infrequently permanent. This, of course, does not apply to progressive lesions in the nature of tumors, involving the pituitary gland.

In these two groups of cases diet and physical therapeutics, with a few exceptions, were purposely eliminated so that whatever results were

obtained could be attributed to organotherapy. The best results have been obtained with the combination of anterior pituitary lobe and thyroid, although cases 11 and 16 (Group A) responded well to anterior pituitary alone, and case 7 (Group A) responded to thyroid plus diet and exercise. The ovarian and testicular hormones are not essential and are of doubtful value.

All chronic infectious foci should be removed before glandular therapy is inaugurated.

Fig. 26. This figure represents the type of case in which fat is redistributed by administration of thyroid and pituitary therapy.

The effect of correcting chronic suppurative sinusitis and organotherapy upon hypopyrexia is illustrated in Figure 27.

In the pluriglandular cases Timme(*a*) has reported remarkable success with whole gland substance in doses of two to four grains three times daily, occasionally using "pituitrin" hypodermically 0.5 to 1 c.c. per day or alternate days for periods of a week or two. He uses the anterior lobe in cases with pronounced genital delay. Stellwagen has employed the anterior lobe successfully in the treatment of impotence, and Tucker in doses of ten to thirty grains reported favorable results in epilepsy. Visual field disturbances, the result of pituitary disease, have been restored to normal by the combined medication of pituitary and thyroid gland substance (de

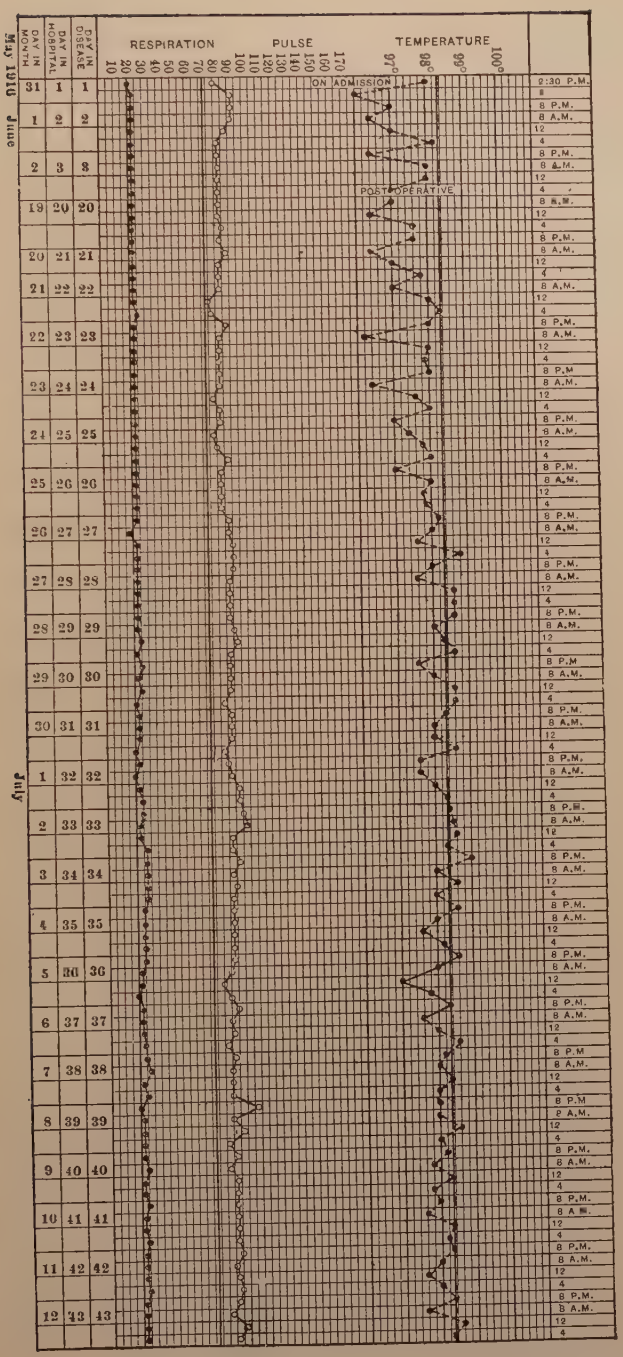


Fig. 27. Chart of a patient suffering with hypophyseal dystrophy, showing the effect on temperature of draining the antrum and administering thyroid and anterior pituitary lobe.

Schweinitz and How) and by pituitary, thyroid and suprarenal gland substance (Timme(*b*)).

For the relief of pituitary headache Pardee recommends the whole gland in doses of one-half to two grains three times a day, decreasing the dose as the headache is relieved. The cachexia which follows destructive lesions of the anterior lobe is favorably influenced by pituitary feeding, especially with the anterior pituitary extract. Occasionally the most annoying symptoms of dystrophia adiposogenitalis are polydipsia and polyuria due to an associated diabetes insipidus. The condition may be transitory, although it is usually permanent. However, the symptoms can be controlled by systematic administration of posterior lobe extract "pituitrin" in 0.5–1 c.c. doses hypodermically. This dose ordinarily controls the thirst and polyuria from one to two days. The same dose given per rectum controls the polyuria for three or four hours (Goetsch). The remarkable effect of "pituitrin" in case XV, Series 1, upon the urinary output is shown in Figure 22. For further information on this subject the reader is referred to the chapter on Diabetes Insipidus.

The effect of anterior lobe feeding upon growth has been emphasized (Goetsch, Cushing, etc.) and Beverly Tucker reported the case of an underdeveloped boy, who grew 7/8 of an inch in five weeks on pituitary feeding.

The dose of liquid extract of the posterior lobe and infundibulum (infundibulin, pituitrin) because of its wide range of therapeutic application has become fairly well established; ordinarily 0.5 to 1 c.c. administered hypodermically, constitutes a dose, although larger doses are not infrequently given. The development of intestinal cramp indicates its physiological limits. Larger doses will produce tachycardia, tremors, etc.

Powdered whole gland may be given in doses ranging two to six grains daily. Both posterior and whole gland substance are contraindicated in conditions of high blood pressure, because of the pressor action of a principle contained in the posterior lobe and infundibulum.

X-Ray.—Although Gramegna (1909) reported a case of acromegaly treated by X-ray, in which the headache was relieved and the visual fields temporarily improved, the subject did not receive general recognition until Béclère (1913) reported four cases in which radiotherapy met with considerable success. In one of his cases headache, dizzines, nausea and vomiting disappeared and the vision improved; the pathologic process in the bones was arrested and the sexual function restored; five years later the patient was reported in good health. In all of his cases there was improvement of the visual fields and in two the headaches completely disappeared.

Others including Calamet, Terrien, Loeb, Darrier, Jaugeas(*a*) and Schäfer(*a*) have reported cases treated with practically the same results.

Radium has been used by Douglas Quick in three cases of hypophyseal tumors but apparently it has no advantage over X-ray.

The field of radiotherapy in pituitary disease is too new and the cases reported are too inadequate to draw any very definite conclusions. However, indications are that it is undoubtedly of value in selected cases of hypophyseal tumors with hyperpituitary symptoms and early states of secondary hypopituitarism or in dyspituitarism with pressure symptoms. The most striking effect is upon the visual fields which have frequently been benefited and in several instances slowly restored to normal. The headache, vertigo and vomiting are often promptly relieved; the adiposis and genital functions have also been favorably influenced. For a description of the technic employed in radiotherapy of pituitary tumors reference should be made to Loeb's article.

General Measures.—These are supplementary to organotherapy and include diet, rest, exercise, massage, hydrotherapy, electrotherapy, etc. They are valuable adjuncts in combating obesity, nervous and mental states, cardiovascular disturbance, and asthenia.

The restriction of carbohydrates and fats helps to reduce the weight of the patient, which is desirable in many instances. However, without recourse to glandular therapy the normal body configuration is not restored, and the results are not permanent. Systematic exercise and massage exert a favorable influence on the fat dystrophy and strengthen the muscles which lack tonicity.

Patients in whom the condition of dystrophia adiposogenitalis existed for a long period generally present severe nervous symptoms frequently mental disturbance, marked asthenia, slow pulse, low blood pressure, subnormal temperature, and increased sugar tolerance. In such cases the best results are obtained by combining organotherapy with a rest cure, in which stress is placed on diet, massage, hydrotherapy, etc., followed by systematic exercise and suitable diversion.

Surgical.—The possibility of successfully removing a pituitary tumor in spite of its deep seated and well protected anatomical situation must be considered one of the greatest achievements of modern surgery. Among the pioneers, who exploited this new domain in surgery may be mentioned Caton and Paul, Horsley, Schloffer(*b*), Hochenegg(*a*), v. Eiselsberg, Cushing(*b*), and Krause.

The application of surgery in dystrophia adiposogenitalis is largely confined to tumors of the hypophysis or to the pressure effect on the gland of a tumor in adjacent areas. There are two operative procedures; viz.,.a radical operation for the removal of the gland and a palliative operation, usually a decompression in cases in which the radical removal is contraindicated. If the tumor is a benign hyperplasia, a radical operation may give indefinite relief from pressure symptoms. In the palliative operation temporary relief follows in many instances, but no attempt is made at cure.

A review of the literature on surgery of the hypophysis emphasizes two points—the wide variation in operative mortality, which, of course, is to be expected, and the relatively small group of cases in which surgery offers anything worth while (Quick). The operative mortality depends upon the experience of the operator in cranial surgery and upon the method or route of approach; ranging from 35 per cent to 10 per cent or less.

Indications for operation in pituitary growth or neighborhood lesions are (a) symptoms due to increased general intracranial pressure, such as headache; (b) symptoms due to local pressure, such as blindness, oculomotor palsy, and "pituitary headache"; (c) symptoms due to disturbance of the pituitary secretion producing acromegaly or dystrophia adiposogenitalis (Bell(*b*)).

The headache and visual disturbances are most markedly benefited by operation. The visual symptoms do not improve if optic atrophy is complete. The adiposity is ordinarily not influenced unless feeding of gland substance is used in conjunction with operation. The skeletal changes, which depend upon metabolic processes and trophic influences are as a rule only slightly benefited.

The following is a list of methods of approach employed by various surgeons, taken from Cope's statistics: superior nasal (von Eiselsberg), inferior nasal (Hirsch), inferior nasal submucous (Cushing), temporal (Horsley, Cushing), orbitofrontal (Frazier, Cushing, Sargent, Cope), orbitonasal (Kahler, Chiari), palatal (Preysing). Cushing(*b*) employed the inferior nasal submucous method in one hundred and six cases with only eight deaths. The various methods and their technique will be discussed in another chapter.

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